UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO ALL CASES

PSC MEMORANDUM IN OPPOSITION TO MOTION TO RECONSIDER AND VACATE CMO 36 AND TO STRIKE GENERAL EXPERTS' IMPROPER TESTIMONY

MAY IT PLEASE THE COURT:

I. Introduction

Without any change in applicable law or authority, Sanofi's motion asks this Court to reconsider concerns previously raised and overruled by this Court. R. Doc. 13981; Case Management Order No. 36, R. Doc. 14925 (hereinafter "CMO 36"). Moreover, the motion attempts to have this Court adjudicate admissibility issues that specifically were preserved, at Sanofi's request and as memorialized in the Order:

> Ultimate determinations as to the admissibility of the preserved expert testimony are subject to the authority of the respective transferor courts. Objections to the relevance or admissibility of testimony or documents used as deposition exhibits are not waived and are preserved pending a later ruling by the Court or by the trial judge.[1]

At multiple conferences with the Court pre- and post-entry of said Order, Sanofi memorialized its position that evidentiary and admissibility issues regarding the preserved general expert testimony should be preserved for the remand courts. Indeed, pursuant to CMO 36, the Court was provided with charts containing evidentiary disclosures and objections thereto in advance of each preservation examination completed thus far. The Court declined to adjudicate such objections, to

[1] CMO 36 at ¶3(c).

preside over the depositions, and to make any evidentiary or admissibility conclusions regarding the testimony or exhibits/demonstratives.

Nonetheless, Sanofi's instant motion now claims it is prejudiced, essentially re-urging the same arguments it made previously to entry of the applicable Order.[2] But, Sanofi's complaints regarding the process were overruled, and the Order was entered; however, ultimate adjudication of the particular issues Sanofi now raises were specifically preserved for the transferor courts on remand. Setting aside the fact that sanofi cannot be prejudiced by preserved sworn testimony that is saved in electronic format, but not yet played to any jury, its motion mischaracterizes the Order as if it pre-allows that preserved testimony to be played, as is, in any trial. The plain language of the Order belies such a characterization.

Furthermore, the parties have committed substantial resources to taking four (4) days of preservation testimony of two (2) of Plaintiffs' expert witnesses (Drs. Madigan and Feigal) – direct, cross and redirect exams for each – as well as a discovery deposition of a third expert witness (Dr. Plunkett) in advance of her preservation examination. Sanofi's suggestion that the "PSC ignored [CMO 36]" in conducting these depositions is absolutely untrue and unsupportable; to the contrary, the PSC properly disclosed the reports and documents on which these experts would base their opinions, and the PSC also timely disclosed materials to be used as exhibits and demonstratives during the depositions. Multiple meet and confers occurred in advance of the depositions, and Sanofi had multiple opportunities (and exercised its right) to address concerns in advance of the preservation examinations. Defendants' current attempt to undo the process, which was carefully considered by the Court to be within the scope of the PSC's obligations to create a

[2] It is worth noting that CMO 36 required Sanofi to pay half of the court reporting charges for the depositions. Despite the PSC's request for payment of same, sanofi has refused to abide by the terms of the order claiming it will catch up when sanofi preserves its own general experts' testimony. *Id.* at ¶5.

trial package for counsel's use on remand, should be denied. Sanofi's requested relief to jettison the entire order is unnecessarily draconian in light of the few examples of testimony it claims is inadmissible out of over 14 hours of preserved testimony.

A. Background

In the Court's recent Suggestion of Remand entered yesterday, the Court summarized its implementation of CMO 36:

> In April 2022, the Court granted the PSC's Motion to Preserve Expert Testimony and later entered CMO 36. CMO 36 set out the protocols to preserve general expert testimony by video for potential use in remanded cases. Under CMO 36, expert preservation deposition testimony is "subject to the Court's prior rulings as they relate to these witnesses," including the Court's Rule 702 rulings. In addition, the Court did not pre-adjudicate issues related to admissibility or availability—for example, whether the parties may introduce preservation deposition testimony at trial. See Fed. R. Evid. 804. The parties have completed the preservation depositions of two of Plaintiffs' experts. Preservation depositions, including depositions of Sanofi's experts, may continue in this Court after the entry of this Order.

R. Doc. 15763 at 14 (footnotes omitted).

As CMO 36 notes, significant discovery – including expert discovery – has been completed in this MDL, and Sanofi has examined each of the PSC's experts on multiple occasions, well in excess of the ordinary limit of seven (7) hours per expert. Following the experts' preservation deposition testimony on direct exam, Sanofi was allowed a full and complete cross-examination. In regard to Dr. Feigal, after a two (2) hour and 42-minute direct examination, Sanofi proceeded with over four (4) hours of cross-examination. Regarding Dr. Madigan, his direct lasted approximately two (2) hours and 50 minutes, while Sanofi's cross-examination lasted over four (4) hours. At no point during its cross-examination of either expert did Sanofi seek Court intervention to address any objections to the content or scope of the testimony.

It was for this very reason that the Court ordered that all "general expert preservation depositions shall take place … at the United States District Court for the Eastern District of Louisiana."[3] The Court already informed the parties that "the ultimate determination as to the admissibility of the preserved expert testimony are subject to the authority of the respective transferor courts."[4] Additionally, many of the issues sanofi raises concerning the testimony of Drs. Feigal and Madigan relate to testimony elicited either on cross-examination or on re-direct, after Sanofi's questioning opened the door to the experts' response.

B. Reconsideration Standard

Because the Federal Rules of Civil Procedure do not specifically authorize motions for reconsideration, and considering Rule 59 and 60 are inapplicable by defendants' own urging, sanofi asks this Court to consider their motion as an interlocutory judgment under Rule 54(b). One of the opinions cited by sanofi states: "The standard for reviewing the vacation of an interlocutory order is hence not whether the stringent Rule 60(b) requirements are met, but is rather whether the district court abused its discretion." *McKay v. Novartis Pharm. Corp.*, 751 F.3d 694, 701 (5th Cir. 2014) (citing *Zimzores v. Veterans Admin.*, 778 F.2d 264, 266 (5th Cir. 1985)). Plaintiffs do not believe the Court abused its discretion by entering CMO 36, after careful consideration of the pleadings and oral argument thereon, followed by joint submission of a mostly agreed upon proposed order.

II. Sanofi's Qualms with the Testimony are Appropriately Preserved for Adjudication by the Transferor/Remand Trial Courts.

The basis and methodology of the respective opinions of Drs. Feigal and Madigan, as elicited on direct examination, have been the subject of repeated FRE 702/*Daubert* challenges, and

[3] CMO 36, ¶ 3(a).
[4] *Id.* at ¶ 3(c).

there should be no need for repeating this costly process.[5] If the transferor courts are inclined to revisit challenges under FRE 702 or *Daubert*, the PSC respectfully suggests that is not an issue for this Court; and, undoubtedly, the parties to any future trials in transferor courts will have the opportunity to shape the boundaries of the evidence through motions *in limine*.

Sanofi's motion entirely discounts the ultimate trial courts' gatekeeping function, and instead rests on the assumption of a sterilized, pre-packaged and objection-free direct examination and cross-examination. This Court has overseen two Taxotere trials, and has experienced both parties object and defend objections, both to their own and their opponent's witnesses. This Court has made trial decisions on those evidentiary challenges. The transferor courts will be called upon to do the same, with the notable exception being that evidentiary decisions on the preserved video testimony will largely be made *prior* to trial.

As a result, Sanofi cannot be prejudiced. The expert testimony preserved is to be used in all remanded cases that fall within the "fence posts" the Court has established, with product usage within 2007 – 2015. Evidence of Sanofi's knowledge, and actions or inactions taken while armed with knowledge, changed over time and what may be admissible in a later case may not be appropriate in earlier cases. Furthermore, whether cross examination opened the door for questioning outside the four corners of an expert's report is an issue for the ultimate trial courts to make when considering those lines of questioning in the context of the particular facts of the case being tried. Thus, thus what is relevant and admissible in any particular case will vary, sometimes widely.

For example, in March 2017 Sanofi ultimately convened a meeting to discuss and implement a label change to include the full TAX316 data concerning the "ongoing alopecia."[6] In

[5] *See* R. Doc. 15763 at 33-34.
[6] Ex. A, TAX 316 CSR; Ex. B, Sanofi_05173852

doing so, it enlisted the assistance of its current defense counsel and in-house counsel overseeing this litigation[7] – the ensuing label change *only* relied upon the TAX 316 CSR, at which time was nearly seven years old. Nothing else was included as a basis for a label change in 2017. It is entirely conceivable a trial court could allow such evidence into any post-2011 case to demonstrate that Sanofi could have, or should have, used the TAX 316 CSR to institute a label update. The issue is one of control and opportunity, not subsequent remedial measure. And this evidence may be further relevant to counter any potential testimony offered by Sanofi through its corporate representatives, such as Michael Kopreski, M.D., or through its experts.

Plaintiffs on remand must have the opportunity to have access the fullest evidence possible from the general experts both that may be admissible in their cases-in-chief, based on their expert reports, and that may be necessary to counter the testimony and tactics that Sanofi may use and employ. To allow otherwise at this point would unnecessarily handcuff plaintiffs and lessen the likelihood of useability of these preservation exams (in lieu of repeated appearances of the same witnesses, the costs and inefficiency of which CMO 36 seeks to avoid).

For the reasons stated here and more particularly explained below, Defendant Sanofi's Motion to Reconsider and Vacate CMO 36 and to Strike should be denied.

III. Sanofi's Allegation that Dr. Feigal Offers Causation Opinions on Other Chemotherapy Options is Without Merit.

On direct examination, Dr. Feigal agrees that she does not have any reliable scientific evidence to support causation for other chemotherapies.[8] She notes that all she saw were anecdotal cases.[9] Sanofi's counsel claims this is improper despite it being consistent with how she has testified before regarding her research, investigation, reliance materials and the foundations of her

[7] Ex. B, Sanofi_05173852 at p. 2.
[8] Ex. C, Feigal Preservation Dep. 1/26/2022, 44:1-45:14.
[9] *Id*. at 45:13-13

report. For example, in her January 11, 2019 deposition, Sanofi's counsel questioned Dr. Feigal concerning "cases of permanent hair loss have been reported with . . ." and Dr. Feigal agrees and adds ". . .anecdotal reports, yes. . . ."[10] Her testimony also is consistent with her trial testimony:

> Q: Now, Dr. Feigal, because this jury has been told that A and C may have caused Ms. Earnest's lack of hair regrowth, I have to ask you, have you reviewed -- in your review of all of the scientific evidence and medical literature that's out there, have you seen evidence that A or C has been related -- causally related to permanent irreversible hair loss, hair that doesn't grow back when it's supposed to?
> A. I haven't seen evidence for causal relationship. You'll see those anecdotal cases that have been reported in the published literature.[11]

In the preservation examination, Sanofi's counsel asks: "Nowhere in your expert report do you say, 'I conducted the analysis and I have determined that Adriamycin cannot cause pCIA?'" Dr. Feigal responds: "I do not have that exact sentence, that's correct." She further qualifies: "[b]ecause there wasn't sufficient data to do that analysis."[12] But, sanofi's counsel does not ask if she has formed that opinion – Dr. Feigal was not asked was: "Dr. Feigal, have you determined that Adriamycin cannot cause PCIA?" Thus, there is nothing inconsistent between her prior testimony and her responses to questions about the foundations of her opinions and the information she reviewed and relied upon.

Again, consistent with her present preserved testimony, Dr. Feigal testified on 11/21/2019 that:

> no one's arguing there may be cases recorded, but there's no – no similar experience with another drug. We don't even – you know, prior to 2001, we actually didn't even start to see permanent chemotherapy induced alopecia with conventional doses of

[10] Ex. D, Feigal Discovery Dep. 1/11/2019, 596:1-597:9; *see also id.* at 599:14-600:10 ("there have been anecdotal patients" (reviewing the Crown abstract)); *see also* Ex. E, Feigal Discovery Dep. 11/21/2019, 241:2-8 ("yes, anecdotal cases. . . I have that in my table (Table 2 of Feigal report).").
[11] Ex. F, Earnest Trial Transcript 9/20/2019, 1211:13-22.
[12] Ex. G, Feigal Preservation Dep. 1/27/2023, 262:8-263:14.

> Taxotere. So, this was a new phenomenon. The AC and CMF, they were around for decades and you didn't have published studies with permanent irreversible alopecia. . . .[13]

When asked "Have you made any effort to analyze why that is the case", Dr. Feigal answered "I did a search of what was publicly available to look at reporting . . . there's nothing different about how people can publish papers with Taxotere as they could have done with Taxol, or AC, or CMF."[14] She also pointed to her review of Dr. Madigan's report and disproportionality analysis, and notes that "… nothing's changed other than [Taxotere] is a new drug."[15]

Moreover, assuming *arguendo* it was beyond the scope of her report (which it is not), robust cross examination on these statements followed.[16] In that cross examination, Dr. Feigal corrected Sanofi's characterization of ruling out or ruling in other chemotherapies as contributing to pCIA. Sanofi attempts to imply that without conducting a Bradford-Hill analysis Dr. Feigal could not rule out other chemotherapy drugs as causes; in addition to conceding she does not make conclusions that other drugs cannot cause pCIA, Dr. Feigal appropriately responds by pointing out the rather obvious scientific point that she cannot analyze data that does not exist.[17] Sanofi was well prepared for cross examination, and sanofi's concerns, at this preservation stage, are premature and lacking in merit.

IV. Sanofi's Complaints Regarding Dr. Feigal's References to Excluded Evidence

The testimony cited in Sanofi's motion does not relate directly to labels, but to its use of a document and counsel's inaccurate description and characterization of what the document

[13] Ex. E, Feigal Discovery Dep. 11/21/2019, 172:14-174:21; *see also* Ex. H, Feigal Discovery Dep. 4/10/2020, 85:6-11 ("I analyzed those drugs in the context of answering the question about Taxotere. I found no evidence to the degree I found it with Taxotere, for general causation. But no, I did not do general causation analysis on any of the other chemotherapy drugs, other than Taxotere.").
[14] *Id.*
[15] *Id.*
[16] Ex. G, Feigal Preservation Dep. 1/27/2023, 263-272.
[17] *Id.* at 262:25-266:24.

represents.[18] The documents at issue (exhibits 22, 23 and 24 to the deposition) include documents familiar to the Court and that were used during both the *Earnest* and *Kahn* trials. Sanofi's use of the exhibits in its questioning during the preservation deposition was open-ended and confusing. Ultimately this led Sanofi's counsel to ask Dr. Feigal "how can you figure out which one's correct?"[19] Sanofi's broad questioning opened the door for Dr. Feigal's accurate and candid response:

> Well, you're talking about apples and oranges. The follow-up that Sanofi did submit to the European agency in response to their question about persistent or long-lasting permanent alopecia came back with 29 and 16. That's Sanofi. I'm not manipulating the numbers. That is what they told the agency. . . In response to the question about permanent alopecia, that was their response. And that's actually what's on their label.[20]

Additionally, the history of Sanofi's representation of the TAX 316 patients with "ongoing," permanent, or persistent alopecia remained, and remains, consistent throughout: from the TAX316 CSR, September 2010; to the European agency, January 2013; to the March 3, 2017, Label Review Committee meeting to include the TAX316 CSR numbers in the label; to the current label.[21] It is precisely this consistency that Sanofi's counsel's questioning asked for, and which Dr. Feigal pointed out. Sanofi cannot have it both ways.

Sanofi's counsel next attempted to have Dr. Feigal agree to go behind the company's locked clinical trial data, to direct her to case report forms; Dr. Feigal clearly and directly disagreed that reviewing case report forms would answer the question of permanent alopecia and insisted that the locked clinical trial data is the only appropriate data to review.[22] Later in its cross-

[18] See *Id.* at 305:2-314:21, generally
[19] *Id*. at 311:18-24.
[20] *Id.* at 312:1-12.
[21] Ex. A, TAX316 CSR, Table 47, Sanofi_00724262; Ex. I, Sanofi_04938203; Ex. B, Sanofi_05173852, respectively; and Ex. J, current Taxotere label.
[22] Ex. G, Feigal Preservation Dep. 1/27/2023, 315:9-23, 319:3-320:8.

examination Sanofi again pressed Dr. Feigal for "the truth," and continued to insinuate that going behind locked clinical trial data was appropriate, and she again disagreed and returned to the consistency of the data represented and analyzed by Sanofi.[23]

It should be noted that Plaintiffs will be permitted to play the testimony of Pierre Mancini, Sanofi's Global Biostatistics Head, who testified consistent with Dr. Feigal's preserved testimony that he and his department *only* analyze locked and validated clinical trial data.[24]

Sanofi's attempts to strike and exclude Dr. Feigal's testimony that was a direct result of Sanofi's insistence on its version of what it will argue to the jury is the "truth" about the TAX316 data; the arguments to the jury that 29 and 16 are not accurate clearly conflicts with statements made by sanofi and with its own head of biostatistics. Dr. Feigal should not, therefore, be precluded from pointing out sanofi's contradictory position. Sanofi's repeated characterization of its own data over time is necessary to place its attorneys' arguments into accurate historical context for the jury to consider.

V. With Regard to Dr. Madigan's Testimony, Sanofi Continues to Conflate Statistical Inference of Causation with "Causation"

Dr. Madigan does not state that Taxotere "causes" pCIA, but rather that there is statistical association and *inference* of causation between docetaxel and permanent chemotherapy-induced alopecia.[25] The Court has ruled, over and over, that Dr. Madigan's testimony regarding statistical association and inferences supporting causation are acceptable under Rule 702 standards.[26] Further, Dr. Madigan characterizes data and analyses data very similar to how Sanofi interprets its own data in its Clinical Study Report, 10-year follow-up. What Sanofi concludes from a review

[23] *Id.* at 320:14-326:12.
[24] Ex. K, Mancini Dep. 3/23/2018, 69:7-23, 104:22-105:12, 206:22-207:4, 221:24-222:23, 329:22-330:6; Ex. L, Mancini Dep. 10/12/2018, 365:20-366:25
[25] Ex. M, Madigan Preservation Dep. 11/14/2022, 73:12-19, 112:12-113:3, 124:20-125:2.
[26] R. Doc. 15763 at 32-33 (summarizing prior rulings regarding Dr. Madigan).

of statistical evidence that "docetaxel with doxorubicin and cyclophosphamide (TAC) offers an efficacy benefit to women with operable, node-positive breast cancer," or in other words that docetaxel (TAC) *causes* a benefit.[27] Dr. Madigan does not say that his statistical analysis establishes a cause-and-effect relationship, but rather that it supports an inference in that direction.

And this is consistent recognized principles of epidemiology and the use of statistics:

> "To understand the need for assessing the role of chance as an alternative explanation of an observed association, it is first necessary to consider the concept of inference. Inference involves making a generalization about a larger group of individuals on the basis of a subset or sample."[28]

And this is exactly what Sanofi, and every sponsor, does in every clinical trial, they make inferences based upon the findings of clinical and observational studies to apply to the larger issue of general causation. Dr. Madigan speaks only to the statistical measures that allow for an inference of causation. It is for another expert, Dr. Feigal, to perform the complete causation analysis. The very same purpose in Sanofi conducting its clinical studies and providing its supporting scientific information (pharmacology, animal studies, phase II, III and IV human studies, and observational studies) to demonstrate or infer a beneficial relationship between its drug and a desirable effect should allow Dr. Madigan to demonstrate same thing with his statistical methods – he is simply pointing out that the evidence is more than a mere association (e.g. – that a rooster crows and the sun rises: two events that entirely unrelated), but rather are statistically related in such a way that an inference of a causal link. He does not, because he cannot, offer an opinion that Taxotere causes PCIA in any person; but he does offer the opinion that there is a statistical correlation that is supportive of an inference of general causation.

[27] Ex A, TAX 316 CSR, 10-year follow-up, 9/9/2010.
[28] Hennekens, et al., Epidemiology in Medicine, p. 243 (1987).

Just as the statistics of science are used in order to establish benefit – inferring a causal connection to a benefit – Dr. Madigan's statistical analyses has routinely been allowed by this Court to be presented before a jury for purposes of inference of a statistical risk or likelihood that is beyond merely an association.

VI. Testimony Regarding Chemo2 is Not a New Opinion

Sanofi is simply incorrect when it alleges that Dr. Madigan offered a new analysis, or new opinion, in his preservation deposition.[29] The testimony with which Sanofi takes issue was not elicited on direct examination; rather, it resulted from cross-examination by Sanofi.[30] Furthermore, Dr. Madigan was previously examined on this topic during one of Sanofi's many discovery depositions of Dr. Madigan.[31] In fact, as a result of Sanofi's November 14, 2019 deposition examination of Dr. Madigan, he went back and looked at the hypothesis offered by Sanofi's counsel to prepare for Sanofi's trial cross-examination, and in fact was cross-examined by Sanofi and testified to this very point during in the *Kahn* trial.[32] Dr. Madigan did not perform an analysis in order to offer any new opinion on his direct testimony (here or in the *Kahn* trial), and as a result did not include any such opinion in any of his reports. It was only through the 11/14/2019 discovery deposition and *Kahn* trial cross-examination of Dr. Madigan *by Sanofi's counsel* that Dr. Madigan looked into the issue that Sanofi opened the door to – chemo2. Plaintiffs' counsel did not attempt to elicit any testimony on direct from Dr. Madigan on his chemo2 analysis. Dr. Madigan's look into chemo2 was prompted by Sanofi's deposition examination, and its repeated attempts at rewriting the history of how Sanofi counted its TAX316 ongoing, permanent,

[29] See p. 11 of Sanofi's Motion to Vacate. "Plaintiffs' counsel also elicited testimony on an analysis Dr. Madigan purportedly conducted, but which appeared nowhere in the expert report provided to Sanofi."
[30] Madigan Preservation Dep. 11/15/2022, 405-407.
[31] *Id.* at 364:3-367:24; *see also* Madigan Preservation Dep. 11/14/2022, 61:5-62:22, 77:10-78:2, 79:12-80:4.
[32] Kahn Trial Transcript 11/16/2021, 1472:2-1473:10.

irreversible alopecia events. Plaintiffs' questioning on the topic of chemo2 during redirect was a result of Sanofi's cross-examination of Dr. Madigan on this topic.[33]

Having examined Dr. Madigan through multiple full-day depositions, including on the topic of secondary, non-docetaxel, chemotherapy (chemo2), and having cross-examined Dr. Madigan on the topic during the *Kahn* trial, and knowing the answer he provided, Sanofi cannot open the door again during Dr. Madigan's preservation deposition and then complain when he remains entirely consistent with his prior testimony. Dr. Madigan's prior consistent testimony is not prejudicial to sanofi, nor is it prejudicial to allow Dr. Madigan, on redirect, to explain why any doubt related to chemo2 is a red herring for the jury.

Dr. Madigan remains consistent with his testimony on cross-examination during the *Kahn* trial. Additionally, testimony concerning chemo2 was elicited on cross-examination and opened the door for response in redirect. The trial courts that will preside over future Taxotere trials where Dr. Madigan's preservation testimony may be played are fully capable of reviewing and permitting appropriate testimony via preserved testimony. Sanofi's concerns are premature and ring hollow. Sanofi will have an opportunity to object to proffered testimony prior to trial, seek to have it excluded, or simply choose not play the door-opening portions that create its angst.

VII. Conclusion

As set forth herein, Sanofi's request to revisit entry of CMO 36, at this late stage with preservation examinations well underway, should be denied, as there are no adequate grounds for reconsideration. Moreover, because of the protections built into CMO 36, Sanofi's request to strike certain testimony should likewise be denied. As the Court noted in its recent Suggestion of

[33] Madigan Preservation Dep., 11/15/2022, 404:23-407:23 (Removing chemo2 patients from both the TAC and FAC arms of the TAX316 study results in a statistically significant difference in the event rates between the treatment arms.)

Remand, "[a]dditional motion practice will likely include case-specific expert challenges under Federal Rule of Evidence 702 [… and] [b]efore trial, receiving courts may also anticipate ruling on case-specific motions in limine and objections to case-specific deposition designations and exhibits."[34] The PSC, therefore, requests that the Court deny Sanofi's motion so that the contemplated preservation examinations can continue.[35]

Dated: April 4, 2023

Respectfully submitted,

/s/ Christopher L. Coffin
Christopher L. Coffin (#27902)
PENDLEY, BAUDIN & COFFIN, L.L.P.
1100 Poydras Street, Suite 2225
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
ccoffin@pbclawfirm.com

Plaintiffs' Co-Lead Counsel

/s/ Karen B. Menzies
Karen Barth Menzies (CA Bar #180234)
GIBBS LAW GROUP LLP
6701 Center Drive West, Suite 1400
Los Angeles, California 90045
Telephone: 510-350-9700
Facsimile: 510-350-9701
kbm@classlawgroup.com

Plaintiffs' Co-Lead Counsel

/s/M. Palmer Lambert
M. Palmer Lambert (#33228)
PENDLEY, BAUDIN & COFFIN, L.L.P.
1100 Poydras Street, Suite 2225
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
plambert@pbclawfirm.com

Plaintiffs' Co-Liaison Counsel

/s/Dawn M. Barrios
Dawn M. Barrios (#2821)
BARRIOS, KINGSDORF & CASTEIX, LLP
701 Poydras Street, Suite 3650
New Orleans, LA 70139
Phone: 504-524-3300
Fax: 504-524-3313
barrios@bkc-law.com

Plaintiffs' Co-Liaison Counsel

[34] R. Doc. 15763 at 45-46.
[35] *Id*. at 14, 37.

PLAINTIFFS' STEERING COMMITTEE

Anne Andrews
Andrews & Thornton
4701 Von Karman Ave., Suite 300
Newport Beach, CA 92660
Phone: (800) 664-1734
aa@andrewsthornton.com

Abby E. McClellan
Stueve Siegel Hanson LLP
460 Nichols Road, Suite 200
Kansas City, MO 64112
Phone: (816) 714-7100
Fax: (816) 714-7101
mcclellan@stuevesiegel.com

J. Kyle Bachus
Bachus & Schanker, LLC
101 W Colfax Ave, Suite 650
Denver, CO 80202
Phone: (303) 222-2222
Fax: (303) 893-9900
kyle.bachus@coloradolaw.net

Karen Barth Menzies
Gibbs Law Group LLP
6701 Center Drive West, Suite 1400
Los Angeles, CA 90045 Phone:
510-350-9700
Fax: 510-350-9701
kbm@classlawgroup.com

Lawrence J. Centola, III
Martzell, Bickford & Centola
338 Lafayette Street
New Orleans, LA 70130
Phone: (504) 581-9065
Fax: (504) 581-7635
lcentola@mbfirm.com

David F. Miceli
David F. Miceli, LLC
P.O. Box 2519
Carrollton, GA 30112
Phone: (404) 915-8886
dmiceli@miceli-law.com

Christopher L. Coffin
Pendley, Baudin & Coffin, L.L.P.
1100 Poydras Street, Suite 2225
New Orleans, Louisiana 70163
Phone: (504) 355-0086
Fax: (504) 355-0089
ccoffin@pbclawfirm.com

Andre M. Mura
Gibbs Law Group LLP
505 14th Street Suite 1110
Oakland, CA 94612
Phone: (510) 350-9717
Fax: (510) 350-9701
amm@classlawgroup.com

Alexander G. Dwyer
Kirkendall Dwyer LLP
440 Louisiana, Suite 1901
Houston, TX 77002
Phone: (713) 522-3529
Fax: (713) 495-2331
adwyer@kirkendalldwyer.com

Rand P. Nolen
Fleming, Nolen & Jez, L.L.P.
2800 Post Oak Blvd., Suite 4000
Houston, TX 77056
Phone: (713) 621-7944
Fax: (713) 621-9638
rand_nolen@fleming-law.com

John Gomez
The Gomez Law Firm, PLLC
655 West Broadway, Suite 1700
San Diego, CA 92101
Phone: (619) 237.3490
Fax: 619.237.3496.
john@thegomezfirm.com

Jessica Perez Reynolds
Pendley, Baudin & Coffin
P.O. Drawer 71
24110 Eden Street
Plaquemine, LA 70765
Phone: (225) 687-6396
Fax: (225) 687-6398
jperez@pbclawfirm.com

Emily C. Jeffcott
Morgan & Morgan
700 S. Palafox Street, Suite 95
Pensacola, FL 32505
Phone: (850) 316-9074
Fax: (850) 316-9079
ejeffcott@forthepeople.com

Darin L. Schanker
Bachus & Schanker
101 W Colfax Ave, Suite 650
Denver, CO 80202
Phone: (303) 222-2222
Fax: (303) 893-9900
dls@coloradolaw.net

Andrew Lemmon
Lemmon Law Firm, LLC
P.O. Box 904 15058 River Road
Hahnville, LA 70057
Phone: (985) 783-6789
Fax: (985) 783-1333
andrew@lemmonlawfirm.com

Hunter J. Shkolnik
Napoli Shkolnik PLLC
360 Lexington Avenue, 11th Floor
New York, NY 10017
Phone: (212) 397-1000
hunter@napolilaw.com

Daniel P. Markoff
Atkins & Markoff Law Firm
9211 Lake Hefner Parkway, Suite 104
Oklahoma City, OK 73120
Phone: (405) 607-8757
Fax: (405) 607-8749
dmarkoff@amalaw.com

Zachary Wool
Barrios Kingsdorf & Casteix, LLP
701 Poydras Street, Suite 3650
New Orleans, LA 70139
Phone: (504) 524-3300
Fax: (504) 524-3313
zwool@bkc-law.com

CERTIFICATE OF SERVICE

I hereby certify that on April 4, 2023, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record who are CM/ECF participants.

/s/ Dawn M. Barrios
DAWN M. BARRIOS

EXHIBIT A

sanofi aventis
Because health matters

CLINICAL STUDY REPORT

COMPOUND: Docetaxel

A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes

10-year follow-up

STUDY NUMBER: TAX316 (EFC6041/BCIRG001)

Study Initiation Date (first patient enrolled): 11-Jun-1997

Study Completion Date (last patient, last follow-up visit): 25-Jan-2010

Phase: 3

Design: Prospective, parallel, nonblinded, randomized, positive-controlled, multinational trial

Study Chairmen: **John Mackey**, MD, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta T6G1Z2 Canada
Miguel Martin, MD, Servicio de Oncologia Medica, Hospital Universitario San Carlos, Ciudad Universitaria - 28040 Madrid, Spain
Charles Vogel, MD, Cancer Research Network, 350 NW 84th Ave. Suite 300, Plantation, Florida 33324 USA

Report Date: 09-Sep-2010

Previous Versions (date): 21-Jan-2004: Second interim analysis at 55 months median follow-up

This study was performed in compliance with Good Clinical Practices, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996, using SOP WW-CLIN-SR-SOP-0013-SD04.

SYNOPSIS

Title of the study:	A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes (10-year follow-up)
Investigator(s):	John Mackey, MD, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta, T6G1Z2 Canada Miguel Martin, MD, Servicio de Oncologia Medica, Hospital Universitario San Carlos, Ciudad Universitaria – 28040 Madrid, Spain Charles Vogel, MD, Cancer Research Network, 350 NW 84th Ave. Suite 300, Plantation, Florida 33324 USA
Study center(s):	112 centers in the following countries: Argentina (3), Austria (1), Brazil (2), Canada (23), Czech Republic (2), Egypt (2), France (1), Germany (1), Greece (1), Hungary (3), Israel (3), Poland (3), Portugal (2), Slovak Republic (1), South Africa (1), Spain (14), Sweden (2), United Kingdom (4), Uruguay (2), and the USA (41)
Publications (reference):	Second interim analysis: Martin M, Pienkowsi T, Mackey J, Pawlicki M, Guastall J, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005;352(22):2302-13.
Study period:	Date first patient enrolled: 11-Jun-1997 Date last patient completed: 25-Jan-2010
Phase of development:	3
Objectives:	*Primary*: To compare disease-free survival (DFS) after treatment with Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) in operable breast cancer patients with positive axillary lymph nodes *Secondary*: To compare overall survival (OS), toxicity, and quality of life between the 2 above-mentioned arms, and to evaluate pathologic and molecular markers for predicting efficacy
Methodology:	Prospective, parallel, nonblinded, randomized, positive-controlled, multinational trial
Number of patients:	Efficacy: 1491 Safety : 1480
Poststudy treatment:	Tamoxifen 20 mg orally daily for 5 years was administered following completion of study treatment to patients with estrogen- and/or progesterone-positive tumors unless there was a contraindication for the use of tamoxifen therapy. Patients who had lumpectomy as their primary surgery underwent postoperative radiation therapy after completion of study treatment. Radiation therapy postmastectomy and/or ipsilateral nodal radiation therapy was prescribed at the discretion of the treating radiation oncologist. This was done according to the guidelines at each institution.
Criteria for evaluation:	Efficacy: Disease-free survival, OS Safety: Adverse events (AEs) reported by the patient or noted by the Investigator; standard hematology and blood chemistry; left ventricular ejection fraction (LVEF)

Statistical methods:

The Kaplan-Meier product limit method was used to calculate the DFS and the OS probability estimates. The log-rank test, stratified for the nodal status (1 to 3 versus 4+ positive nodes), was used to compare the 2 treatment groups for both DFS and OS as per the Closed Testing Procedure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from a proportional hazards Cox regression model. All efficacy analyses were conducted in the intent-to-treat (ITT) population; all randomized patients were analyzed in their group and stratum of randomization.

For all safety analyses, only descriptive methods were used without any formal statistical tests of hypotheses. All safety analyses were conducted on all patients who started at least 1 infusion of the study treatment, and patients were analyzed in the treatment groups according to the treatment they actually received.

Summary:

An interim study report (dated 21 January 2004) was included in the dossier submitted in March 2004 and was based on the second interim analysis of TAX316 with cut-off dates of 30 April 2003 and 15 July 2003 for safety and efficacy data, respectively. This analysis demonstrated that TAX316 was statistically significant in favor of TAC for the primary efficacy endpoint of DFS as well as the secondary endpoint of OS in the ITT population. The magnitude of the benefit was clinically significant and remained so even when differences in toxicity were considered. This final study report presents the results of the final analysis of TAX316 after 10 years of follow-up, as summarized below.

Case 2:16-md-02740-JTM-MBN Document 11357-1 Filed 11/04/23 Page 4 of 83

Efficacy results:

At the cut-off date of 11 March 2010, there were a total of 620 DFS events, with 287 and 333 events in the TAC and FAC treatment groups, respectively. TAC was associated with a 20.5% relapse risk reduction compared to FAC (HR = 0.795, 95% CI: 0.679-0.932). The distribution of DFS was significantly different between the 2 treatment groups using the stratified log-rank test on the number of axillary lymph nodes involved at randomization (log-rank p-value = 0.0043).

In the stratum "1 to 3 positive nodes", TAC was associated with a 27.6% relapse risk reduction compared to FAC (HR = 0.724, 95% CI: 0.578-0.907). This difference was statistically significant (p = 0.0047). In the stratum "4 and more positive nodes", TAC was associated with a 12.9% relapse risk reduction compared to FAC (HR = 0.871, 95% CI: 0.0.698-1.088). This risk reduction was not statistically significant (p = 0.223). The treatment by nodal status interaction was not statistically significant (p = 0.259), indicating that the treatment effects were not substantially different between patients with 1 to 3 positive nodes and 4+ positive nodes.

There were 429 deaths (TAC: 188; FAC: 241). TAC was associated with a 25.8% risk reduction in mortality compared to FAC (HR = 0.742, 95% CI: 0.613-0.898). The distribution of OS was significantly different between the 2 treatment groups using the log-rank test stratified on the number of axillary lymph nodes involved at randomization (log-rank p-value = 0.0020).

In the stratum "1 to 3 positive nodes", TAC was associated with a 38.4% risk reduction in mortality compared to FAC (HR = 0.616, 95% CI: 0.464-0.819). The difference was statistically significant (p = 0.0008). In the stratum "4 and more positive nodes", the risk reduction in mortality associated with TAC was not statistically significant (HR = 0.866, 95% CI: 0.668-1.122, p = 0.2746). The treatment by nodal status interaction reached a significance level of p = 0.0814. This value was below the threshold of 0.15 defined in the statistical analysis plan, indicating that there was some variability in the results of these 2 subgroups.

Overall, for both DFS and OS, the subgroup analyses demonstrated a consistent benefit for TAC over FAC.

Second primary malignancies (SPMs) were reported in this study primarily as efficacy endpoints, either as the first primary DFS event (ie, an SPM that occurred prior to breast cancer relapse) or as an efficacy endpoint (ie, an SPM that occurred after the first primary DFS event [breast cancer relapse or an SPM]). In some instances, SPMs were also reported as serious adverse events.

Of the SPMs reported as efficacy events, 109 SPMs were reported as DFS events (TAC: 56 [19.5%] events; FAC: 53 [15.9%] events). These included contralateral breast cancer (the most common subtype) reported in 30 patients (TAC: 15; FAC: 15) and ipsilateral breast cancer reported in 2 patients (TAC: 0; FAC: 2). There were also 5 reports of leukemia: 4 acute myeloid leukemia (TAC: 4; FAC: 0), and 1 chronic lymphocytic leukemia (TAC: 0; FAC: 1). Of the 36 SPMs reported after a primary DFS event, 17 events occurred in 15 TAC patients and 19 events occurred in 17 FAC patients. These included 8 reports of contralateral breast cancer (TAC: 3; FAC: 5), and 1 report of acute myeloid leukemia (TAC: 0; FAC: 1). Therefore, a total of 145 SPM events (TAC: 73; FAC: 72) were reported as efficacy endpoints.

Ten SPMs were reported as serious adverse events (TAC: 6; FAC: 4), of which 8 were also considered efficacy endpoints (TAC: 6; FAC: 2). Five of the 6 cases of leukemia were reported as TEAEs and there were 3 reports of myelodysplastic syndrome (TAC: 2; FAC: 1).

In summary, 147 SPM events (TAC: 73; FAC: 74) were reported as either efficacy and/or safety events. Overall, these occurred in 67 TAC patients and in 68 FAC patients (due to multiple SPM events occurring in some patients).

Safety results:

Of the 1491 randomized patients in the study, 1480 patients were treated with study drugs. Almost all treated patients (>99%) experienced at least 1 treatment-emergent adverse event (TEAE) during study treatment. Grade 3 to 4 TEAEs (TAC: 36.7%; FAC: 26.9%), serious TEAEs (TAC: 35.9%; FAC: 9.1%), and serious Grade 3 to 4 TEAEs (TAC: 10.1%; FAC: 4.9%) were reported more frequently in TAC patients during chemotherapy. Safety during the treatment period was previously reported in detail in the interim study report (Appendix 14.1.1).

The focus of this 10-year final report is the follow-up period (ie, >30 days after the last administration of study drugs), for which new safety information is presented.

In the follow-up period, the incidence of Grade 3 to 4 AEs (TAC: 13.8%; FAC: 11.3%) was higher in the TAC group.

Of the TEAEs persisting into the follow-up period, the most common in both treatment groups were alopecia (TAC: 92.3%; FAC: 87.6%), asthenia (TAC: 31.7%; FAC: 24.5%), and amenorrhea (TAC: 27.2%; FAC: 17.0%). Amenorrhea was reported as persisting into the follow-up period in 198 of 420 (47.1%) premenopausal patients in the TAC group and in 119 of 403 (29.5%) premenopausal patients in the FAC group. Among TEAEs that persisted into the follow-up period in >1% of patients, the majority of events resolved; however, amenorrhea remained ongoing in 59.9% of TAC patients and 68.8% of FAC patients.

The types and incidence rates of AEs starting or worsening in the follow-up period were similar in both treatment groups, with the exception of peripheral sensory neuropathy (TAC: 3.8%; FAC: 0.7%), which was more frequently reported in the TAC group.

Serious TEAEs were reported more frequently in TAC patients during the follow-up period (TAC: 7.1%; FAC: 4.5%). Among the 1480 treated patients, 189 (25.4%) TAC patients and 242 (32.9%) FAC patients died, and most of the deaths occurred in the follow-up period with the majority due to breast cancer. There were 10 fatal outcomes (TAC: 4; FAC: 6) considered related to study drugs, of which 8 occurred in the follow-up period. The most common cause of related death was congestive heart failure (CHF).

In total, 26 patients in the TAC group and 17 patients in the FAC group were reported to have developed CHF at some point during the study period, with most cases reported in the follow-up period. The difference in the incidence of CHF between the 2 treatment groups was not statistically significant.

Second primary malignancies were reported either as the first primary DFS event (ie, an SPM that occurred prior to breast cancer relapse) or as an efficacy endpoint (ie, an SPM that occurred after the first primary event [breast cancer relapse or an SPM]; these SPMs reported as DFS events are summarized under “Efficacy results.” Ten SPMs were reported as serious adverse events (TAC: 6; FAC: 4), of which 8 were also considered efficacy endpoints (TAC: 6; FAC: 2).

Conclusions:

The results of this study show that docetaxel in combination with doxorubicin and cyclophosphamide (TAC) offers an efficacy benefit to women with operable, node-positive breast cancer. The safety profile of TAC was manageable and consistent with the known toxicity of the individual drugs and of the TAC regimen. These final results from 10 years of follow-up continue to support the use of TAC as an appropriate adjuvant chemotherapy option in women with operable, node-positive breast cancer.

Date of report: 09-Sep-2010

Page 5

TABLE OF CONTENTS

SYNOPSIS **2**

TABLE OF CONTENTS **6**

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **10**

2 ETHICAL CONSIDERATIONS **11**

3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE **12**

4 INTRODUCTION **13**

5 STUDY OBJECTIVES **14**

6 INVESTIGATIONAL PLAN **15**

6.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN 15

6.2 DEFINITION AND TIMING OF ASSESSMENTS 15

6.3 STATISTICAL AND ANALYTICAL PROCEDURES 15

6.3.1 Efficacy analyses 15

6.3.2 Safety 16

6.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES 18

7 STUDY PATIENTS **19**

7.1 DISPOSITION OF PATIENTS 19

8 EFFICACY EVALUATION **20**

8.1 PRIMARY ANALYSIS ON DISEASE-FREE SURVIVAL 20

8.2 OVERALL SURVIVAL ANALYSIS 30

9 SAFETY EVALUATION **34**

9.1 EXTENT OF EXPOSURE 34

9.2 POPULATION DEMOGRAPHICS 34

9.3 ADVERSE EVENTS 34

9.3.1 Summary of occurrence of adverse events 34

9.3.2 Adverse events during treatment period 35

9.3.3 Adverse events during follow-up 36

9.3.4 Deaths, serious adverse events, and other significant adverse events 44

9.3.4.1 Deaths 44
9.3.4.2 Serious adverse events 52
9.3.4.3 Adverse events leading to withdrawal 53
9.3.5 Analysis of adverse events by age and race 53
9.4 CLINICAL LABORATORY EVALUATIONS 53
9.5 SPECIAL SAFETY 54
9.5.1 Cardiovascular 54
9.5.2 Second primary malignancies 66
9.5.3 Other special safety 68
9.6 SAFETY CONCLUSIONS 68
10 PHARMACOKINETIC EVALUATION 70
11 DISCUSSION AND OVERALL CONCLUSIONS 71
12 REFERENCES 72
13 SUPPORTIVE INFORMATION 73
13.1 DEMOGRAPHIC DATA 73
13.2 EFFICACY DATA 73
13.3 SAFETY DATA 73
13.3.1 Listing of narratives of deaths, serious adverse events, and other significant adverse events 73
13.4 PHARMACOKINETIC DATA 78
14 APPENDICES 79

LIST OF TABLES

Table 1 – Disease-free survival per axillary lymph nodes in all randomized patients, by randomization group – ITT analysis 21

Table 2 – Disease-free survival - summary of reasons for censoring – ITT population 22

Table 3 – Disease-free survival - first primary events, by type of event – ITT population 23

Table 4 – Number of patients with other second primary malignancies occurring after a primary DFS event, by type of event – ITT population 26

Table 5 – Overall survival by axillary lymph nodes in all randomized patients, by randomization group – ITT analysis 31

Table 6 – Overview of patients with adverse events regardless of causal relationship, by study period – safety population 35

Table 7 – Number (%) of patients with TEAEs during the treatment period (incidence ≥2% in TAC) that persisted into the follow-up period, regardless of causal relationship – safety population 37

Table 8 – Number (%) of patients with adverse events starting or worsening in follow-up, by causality (for adverse events related to study drugs in >1 patient in either treatment group) – safety population 40

Table 9 – Outcome in patients with adverse events starting or worsening in follow-up, regardless of causal relationship (incidence ≥0.5% in the TAC group) – safety population 42

Table 10 – Number (%) of all deaths occurring by cause of death during study period – safety population 45

Table 11 – Deaths due to causes other than breast cancer, occurring >30 days after last administration of study drugs, by causality – safety population 47

Table 12 – Overview of serious adverse events by study period, regardless of causal relationship – safety population 52

Table 13 – Number (%) of patients with cardiac TEAEs during the treatment period, overall and by severity grading (worst grade reported), regardless of causal relationship – safety population 55

Table 14 – Number (%) of patients with cardiac TEAEs starting or worsening in the follow-up period, overall and by severity grading (worst grade reported), regardless of causal relationship – safety population 57

Table 15 – Number (%) of patients with congestive heart failure, during study period – safety population . 59

Table 16 – Cumulative incidence of congestive heart failure 60

Table 17 – Risk factors for congestive heart failure during the study period – safety population 63

Table 18 – Congestive heart failure incidence and risk factors during the study period – safety population 64

Table 19 – Number (%) of patients with relative decrease of LVEF, by evaluable patients, during study period – safety population 65

Table 20 – Summary of second primary malignancies reported as adverse events 67

Table 21 – Listing of patients with events in the follow-up period reported in the interim clinical study report narratives 74

Table 22 – Listing of patients with events in the follow-up period reported in the final clinical study report narratives 76

LIST OF FIGURES

Figure 1 – Disease-free survival, by randomization group – ITT analysis 20
Figure 2 – Forest plot for disease-free survival, main subgroup analysis – ITT population 28
Figure 3 – Forest plot for disease-free survival subgroup analysis, other baseline characteristics – ITT population 29
Figure 4 – Overall survival – ITT analysis 30
Figure 5 – Forest plot for overall survival, main subgroup analysis – ITT population 32
Figure 6 – Forest plot for overall survival subgroup analysis, other baseline characteristics – ITT population 33
Figure 7 – Cumulative incidence of congestive heart failure, time to cardiac event 61
Figure 8 – Incidence of congestive heart failure – hazard function (Kernel method) 62

Page 9

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase (same as SGPT)
AST	aspartate aminotransferase (same as SGOT)
cGy	centi-Gray units
CHF	congestive heart failure
CI	confidence interval
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
DCIS	ductal carcinoma in situ
DFS	disease-free survival
ECG	electrocardiogram
EF	ejection fraction
FAC	5-fluorouracil in combination with doxorubicin and cyclophosphamide
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
ITT	intent-to-treat
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NC/SD	no change/stable disease
NE	not evaluable
OS	overall survival
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SPM	second primary malignancy
TAC	Taxotere® in combination with doxorubicin and cyclophosphamide
TAF	docetaxel, doxorubicin, and 5-fluorouracil
TEAE	treatment-emergent adverse event
US	United States

Page 10

2 ETHICAL CONSIDERATIONS

The protocol and its amendments were submitted to, and approved by, the appropriate ethical review process as described in the interim study report (Appendix 14.1.1).

3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Information on the Investigators and the study administrative structure is available in the interim study report (Appendix 14.1.1, Section 4). Additions or changes to information on the Investigators since the interim study report are presented in Appendix 14.1.2.

4 INTRODUCTION

An interim analysis study report for TAX316 (EFC6041/BCIRG001) was completed 21 January 2004, and was based on the second interim analysis of TAX316 data, with cut-off dates of 30 April 2003 and 15 July 2003 for safety and efficacy data, respectively. At the time of that analysis (at a median follow-up of 55 months), there were 399 disease-free survival (DFS) events.

The second interim analysis presented in the interim study report demonstrated that the results of TAX316 were statistically significant in favor of Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide (TAC) for the primary efficacy endpoint of DFS as well as the secondary endpoint of overall survival (OS) in the intent-to-treat (ITT) population. The greater benefit of TAC over 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) applied irrespective of nodal or hormone receptor status. The magnitude of the benefit was clinically significant, the safety profile was manageable, and these results supported a positive benefit risk ratio for this regimen. The complete study report based on the second interim analysis is provided in Appendix 14.1.1, and contains a full introduction to the study (Appendix 14.1.1, Section 1).

The approval for the adjuvant treatment of patients with operable node-positive breast cancer with TAC was obtained in the United States (US) in August 2004, followed by approval in Europe in November 2004. Subsequently followed by the approval in Canada (December 2006).

All 3 health authorities (The Committee for Medicinal Products for Human Use, the US Food and Drug Administration, and Health Canada) agreed to the submission of a final report after 10 years of follow-up.

This final study report presents the results of the final analysis of TAX316 after 10 years of follow-up.

5 STUDY OBJECTIVES

The primary study objective was to compare DFS after treatment with TAC or FAC in operable breast cancer patients with positive axillary lymph nodes.

The secondary objectives of this study were to:

- compare overall survival between the 2 above-mentioned arms
- compare toxicity and quality of life between the 2 above-mentioned arms
- evaluate pathologic and molecular markers for predicting efficacy
- conduct an independent socioeconomic study in parallel with the clinical study

Page 14

6 INVESTIGATIONAL PLAN

6.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

The complete description of the study design and plan is presented in the interim study report (Appendix 14.1.1, Section 5).

This final study report presents the results of the final analysis of TAX316 after 10 years of follow-up.

6.2 DEFINITION AND TIMING OF ASSESSMENTS

The definition and timing of assessments is presented in the interim study report (Appendix 14.1.1, Section 5.5).

6.3 STATISTICAL AND ANALYTICAL PROCEDURES

The final 10-year analyses were conducted in accordance with the statistical analysis plan (SAP) version 3.0 dated 28 February 2002 (Appendix II.A of Appendix 14.1.1), unless otherwise mentioned in the following sections. The cut-off date for data inclusion in this analysis was 11 March 2010.

6.3.1 Efficacy analyses

Disease-free survival was the primary efficacy endpoint, defined as the time interval between the date of randomization and the date of local, regional, or metastatic relapse, or the date of second primary cancer, or death from any cause, whichever occurred first. If none of these events was reported for a given patient, the DFS time was censored as follows:

- date of the 10-year follow-up visit, if the patient attended
- date of last known/available follow-up visit when the patient was lost to follow-up

The 10-year follow-up visit was the last follow-up visit, occurring 120 months after the last administration of study drugs (a range of 4 months was allowed, meaning that it should have occurred at least 116 months after the last administration of study drugs).

Overall survival was the main secondary endpoint, defined as the time interval between the date of randomization and the date of death or last contact. If death was not reported at the date of the 10-year follow-up visit, the OS time was censored at that date.

Page 15

Disease-free survival and OS were analyzed using the log-rank test, stratified for the nodal status (1 to 3 versus 4+ positive nodes) as per the Closed Testing Procedure described in the SAP. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from a proportional hazards Cox regression model. All efficacy analyses were conducted in the ITT population, for which all randomized patients were analyzed in their group and stratum of randomization.

Reason for censoring, type of first primary event, location of second primary malignancies (SPMs), and cause of death were also presented.

Confirmatory and sensitivity analyses

The analyses of DFS and OS were repeated on different populations using different models to assess the robustness of the results and summarized by the p-value and the HR of TAC versus FAC and the 95% CI, as follows:

- Kaplan-Meier analysis by hormonal receptor status and by nodal status
- Univariate Cox model analysis on the baseline characteristics
- Adjusted and unadjusted interaction analyses between treatment and number of positive axillary node and hormonal receptor status
- Covariate adjusted analysis: multivariate Cox model analysis adjusted on the main prognostic variables (age, histopathological grade, human epidermal growth factor receptor 2 [HER2] status, hormonal receptor status, and tumor size) for each positive axillary node subgroups ([1 to 3] and [4+]).

Subgroup efficacy analyses

Subgroup analyses were performed for the following covariates: nodal status, hormone receptor status, HER2 status, and menopausal status as well as age, tumor size, Karnofsky performance status, surgery, radiotherapy, histological grade, and histological subtype.

6.3.2 Safety

The safety analyses were conducted on all patients who started at least 1 infusion of the study drugs, and patients were analyzed in the treatment group according to the treatment they actually received. All patients who received any dose of docetaxel during the treatment period were included in the TAC group.

For this safety evaluation, "treatment period" is defined as the period from the date of randomization until 30 days after the last administration of study drugs. "Follow-up period" is defined as the period of time beginning after the end of the treatment period (ie, >30 days after the last administration of study drugs) and ending at the completion of the 10-year follow-up period. The term "study period" refers to the entire study period, and includes both the treatment and follow-up periods.

Adverse events (AEs) were assessed in general and also using the concept of treatment-emergent adverse events (TEAEs). A TEAE was defined as any AE not present prior to the start of

treatment and beginning during the treatment period, or any AE already present at the start of treatment and worsening in intensity during the treatment period.

For this 10-year final report, AE terms were recoded from National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 1.0 classification and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) into Medical Dictionary for Regulatory Activities (MedDRA), version 12.1. In addition, some conventions used in the interim study report (eg, adding laboratory safety parameters to the AE tables) were not repeated in this final report.

All AEs, related AEs, and serious adverse events (SAEs) occurring during the treatment and follow-up periods, and TEAEs leading to discontinuation were summarized.

Deaths occurring during the study period were also presented. Reported deaths that occurred after the 10-year follow-up visit were listed and referenced in the relevant tables.

Hematological toxicity was evaluated during the treatment period by assessing incidence of leukopenia, neutropenia, thrombocytopenia, and anemia (graded according to the NCI-CTC, version 1.0 classification), as well as febrile neutropenia, neutropenic infection, and infection.

In addition to hematological laboratory results, biochemical laboratory results were evaluated during the treatment period by assessing total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and creatinine clearance (if indicated) graded according to the NCI-CTC, version 1.0 classification.

Special safety

Special attention was given to cardiovascular AEs and to SPMs.

The following analyses were conducted to further characterize cardiovascular AEs:

- Summary of the numbers of patients experiencing a cardiac AE (MedDRA system organ class (SOC) = "Cardiac disorders") for the treatment and follow-up periods, overall, and by severity grading
- Decrease and relative decrease in left ventricular ejection fraction (LVEF) analyses for evaluable patients, classified according to the percentage of decrease
- Congestive heart failure (CHF): As per the SAP, CHF was previously collected as the NCI term "Cardiac function", Grade 3 to 4. Using MedDRA, CHF is coded by the MedDRA preferred term (PT) "Cardiac failure congestive", Grade 3 to 4.
  - The cumulative incidence of CHF was plotted using a Kaplan-Meier curve. An associated table provides the probability of occurrence of CHF during the treatment and follow-up periods using 12-month intervals starting from randomization.
  - The incidence of CHF was also analyzed according to risk factors including age, weight, history of hypertension, diabetes, hypercholesterolemia, hyperlipidemia, cardiomyopathy, baseline LVEF, and previous radiation therapy on cardiac area.

– The number (%) of patients with relative decrease of LVEF (from baseline), by evaluable patients with CHF, was summarized for the study period.

Second primary malignancies were summarized according to the Case Report Form, and upon medical review, were classified into different types of cancers.

Other specific safety outcomes were also analyzed in order to update the results on fluid retention (MedDRA terms oedema, weight increased, pericardial effusion, and pulmonary oedema), gastrointestinal toxicities (SOC = "gastrointestinal disorders"), neurotoxicity (SOC = "nervous system disorders"), pulmonary toxicity (SOC = "respiratory, thoracic, and mediastinal disorders"), and skin toxicity (SOC = "skin and subcutaneous tissue disorders").

6.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Revisions to the administrative appendices since the time of the interim study report are provided in Appendix 14.1.2.

7 STUDY PATIENTS

7.1 DISPOSITION OF PATIENTS

Of the 1491 randomized patients, 11 did not receive any study drugs: 1 in the TAC group (Patient No.) and 10 in the FAC group (Patients No.). Eight (8) withdrew consent, 1 was lost to follow-up, and 2 did not receive treatment for other reasons (Appendix 14.1.1, Table 1.01-b of Appendix II.F.1). In total, therefore, 1480 patients were treated with study drugs and are included in the safety analysis (TAC: 744; FAC: 736).

One patient randomized to the TAC group (Patient No) received a combination of docetaxel, doxorubicin, and 5-fluorouracil (TAF) for the first 3 cycles by error followed by 3 cycles of TAC. She is analyzed for efficacy and safety in the TAC group.

A full description of patient disposition is found in the interim study report (Appendix 14.1.1, Section 6.1).

Among the 1480 patients treated with study drugs, 82 patients were lost to follow-up at the end of the study, with an actual median follow-up time equal to 96 months.

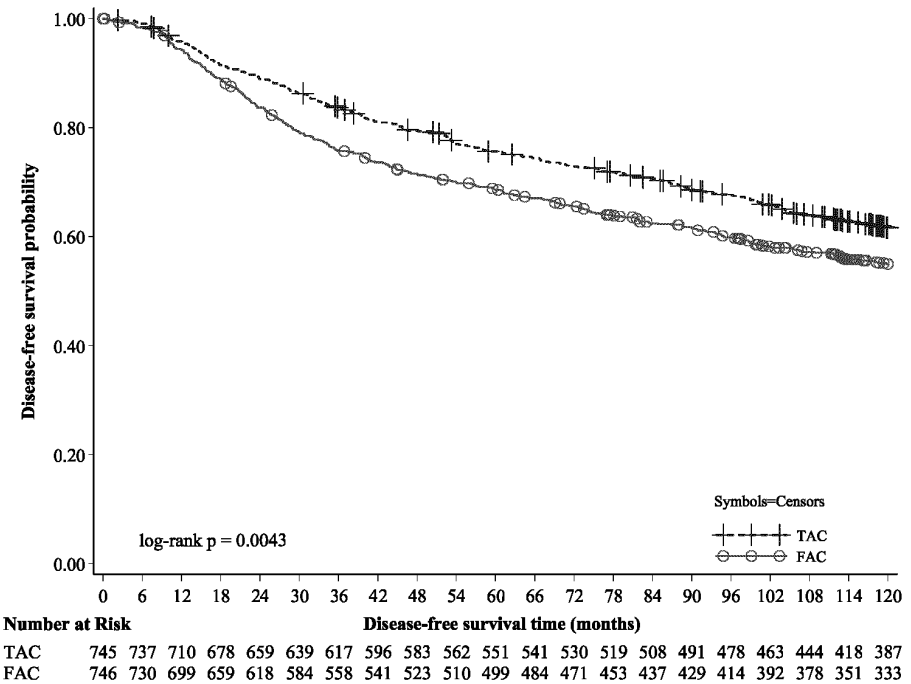
Page 19

8 EFFICACY EVALUATION

8.1 PRIMARY ANALYSIS ON DISEASE-FREE SURVIVAL

At the cut-off date of 11 March 2010, there were a total of 620 DFS events (TAC: 287; FAC: 333). TAC was associated with a 20.5% relapse risk reduction compared to FAC (HR = 0.795, 95% CI: 0.679-0.932). The distribution of DFS was significantly different between the 2 treatment groups using the stratified log-rank test on the number of axillary lymph nodes involved at randomization (log-rank p-value = 0.0043) (Figure 1 and Table 1).

Figure 1 – Disease-free survival, by randomization group – ITT analysis



FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs01_KMPlot_ovrl.sas OUT=REPORT/OUTPUT/a6_dfs01_KMPlot_ovrl_i.rtf (21JUN2010 - 19:27)

In accordance with the closed testing procedure presented in the protocol, the DFS analysis was subsequently performed within each of the 2 strata "1 to 3 positive nodes" and "4 and more positive nodes" (Table 1).

Table 1 – Disease-free survival per axillary lymph nodes in all randomized patients, by randomization group – ITT analysis

Number of positive nodes	Statistics	TAC	FAC
All	Overall number assessed	745	746
	Overall number of events, n (%)	287 (38.5%)	333 (44.6%)
	Timepoint 36 months		
	Probability of surviving (95% CI) [a]	0.837 (0.810-0.863)	0.757 (0.726-0.788)
	Timepoint 60 months		
	Probability of surviving (95% CI) [a]	0.756 (0.725-0.787)	0.687 (0.654-0.720)
	Timepoint 120 months		
	Probability of surviving (95% CI) [a]	0.615 (0.579-0.650)	0.550 (0.513-0.586)
	Stratified log-rank test p-value [b]	0.0043	
	Adjusted Hazard ratio (95% CI) [c]	0.795 (0.679-0.932)	
1-3 Nodes	Overall number assessed	467	459
	Overall number of events, n (%)	137 (29.3%)	170 (37.0%)
	Timepoint 36 months		
	Probability of surviving (95% CI) [a]	0.903 (0.876-0.930)	0.812 (0.776-0.848)
	Timepoint 60 months		
	Probability of surviving (95% CI) [a]	0.831 (0.797-0.865)	0.748 (0.709-0.788)
	Timepoint 120 months		
	Probability of surviving (95% CI) [a]	0.708 (0.666-0.750)	0.630 (0.585-0.675)
	Unstratified log-rank test p-value	0.0047	
	Unadjusted Hazard ratio (95% CI)	0.724 (0.578-0.907)	
≥4 Nodes	Overall number assessed	278	287
	Overall number of events, n (%)	150 (54.0%)	163 (56.8%)
	Timepoint 36 months		
	Probability of surviving (95% CI) [a]	0.725 (0.672-0.777)	0.667 (0.612-0.722)
	Timepoint 60 months		
	Probability of surviving (95% CI) [a]	0.631 (0.574-0.688)	0.587 (0.530-0.645)
	Timepoint 120 months		
	Probability of surviving (95% CI) [a]	0.459 (0.400-0.519)	0.418 (0.359-0.477)
	Unstratified log-rank test p-value	0.2229	
	Unadjusted Hazard ratio (95% CI)	0.871 (0.698-1.088)	
Treatment by nodal status interaction	Unadjusted Interaction	1.2 (0.875-1.645)	p=0.259

[a] Kaplan-Meier estimates

[b] Pairwise stratified log-rank test on the number of positive axillary nodes as per randomization

[c] Estimated using Cox proportional Hazard Model adjusted on the number of positive axillary nodes as per randomization

CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.

Adapted from PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs_main2.sas OUT=REPORT/OUTPUT/a6_dfs_main2_i.rtf (21JUN2010 - 19:51)
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs_main_node2.sas OUT=REPORT/OUTPUT/a6_dfs_main_node2_i.rtf (21JUN2010 - 20:05)
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs_int_posnod2.sas OUT=REPORT/OUTPUT/a6_dfs_int_posnod2_i.rtf (21JUN2010 - 19:35)

In the stratum "1 to 3 positive nodes", there were 137 (29.3%) and 170 (37.0%) events in the TAC and FAC treatment groups, respectively. TAC was associated with a 27.6% relapse risk reduction compared to FAC (HR = 0.724, 95% CI: 0.578-0.907). This difference was statistically significant (p = 0.0047).

In the stratum "4 and more positive nodes", there were 150 (54.0%) and 163 (56.8%) events in the TAC and FAC treatment groups, respectively. TAC was associated with a 12.9% relapse risk

Page 21

reduction compared to FAC (HR = 0.871, 95% CI: 0.0.698-1.088). This risk reduction was not statistically significant (p = 0.223).

The treatment by nodal status interaction was not statistically significant (p = 0.259), indicating that the treatment effects were not substantially different between patients with 1 to 3 positive nodes and 4+ positive nodes. In both subgroups, the DFS rates favored TAC over FAC; however, the treatment difference was greater in patients with 1 to 3 positive nodes (7.8% at 10 years) than 4+ positive nodes (4.1% at 10 years).

The reasons for censoring the DFS analysis are described in Table 2. Eighty-two (82) patients were lost to follow-up (TAC: 43; FAC: 39); for these patients, the median time in follow-up was 107.1 months for TAC, 83.1 months for FAC, and 96.6 months across both groups (Appendix 14.2.6.6, Appendix 14.2.6.8). A total of 415 patients in the TAC group and 374 patients in the FAC group were censored at the time of their 10-year follow-up visit with no documentation of a DFS event occurring at that time. Among these 789 patients, 3 patients (TAC: Patient No[redacted] FAC: Patients No.[redacted]) had events reported after the 10-year follow-up visit. Thus, there were 786 patients (TAC: 414; FAC: 372) with no documentation of breast cancer relapse, SPM, or death. All patients free of event at the time of their 10-year follow-up visit were censored in the DFS analysis. Summaries of reasons for censoring by age, race, and menopausal status can be found in Appendix 14.2.6.1.14.3, Appendix 14.2.6.1.15.3, and Appendix 14.2.6.1.16.3.

Table 2 – Disease-free survival - summary of reasons for censoring – ITT population

	TAC (N=745)	FAC (N=746)
Disease-free survival		
No documentation of BCR, SPM, or death	414 (55.6%)	372 (49.9%)
Event reported after 10-yrs FUP visit date	1 (0.1%)	2 (0.3%)
Lost to follow-up	43 (5.8%)	39 (5.2%)

BCR: breast cancer relapse, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, FUP: follow-up, ITT: intent-to-treat, SPM: second primary malignancy, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs04_rsn_cens.sas OUT=REPORT/OUTPUT/a6_dfs04_rsn_cens_i.rtf (21JUN2010 - 19:52)

The occurrence of an SPM (defined in the protocol as histopathologically proven cancer, excluding nonmelanomatous skin cancer, in situ carcinoma of the cervix, and in situ carcinoma of the breast) was considered to be an efficacy event. In the study, nonmelanomatous skin cancer, ductal carcinoma in situ (DCIS), or cancer that was not histopathologically proven, were sometimes reported as SPMs, not according to the protocol. These events were conservatively retained as SPMs. Second primary malignancies were reported as primary efficacy endpoints (DFS events) if they occurred prior to breast cancer relapse and are summarized in Table 3.

Table 3 – Disease-free survival - first primary events, by type of event – ITT population

	TAC (N=745)	FAC (N=746)
Number of patients		
Event-free patients	458 (61.5%)	413 (55.4%)
Patients with primary event (breast cancer relapse, second primary malignancy, death) [a, b]	287 (38.5%)	333 (44.6%)
Primary events		
Breast cancer relapse	216 (75.3%)	264 (79.3%)
Second primary malignancy	56 (19.5%)	53 (15.9%)
Contralateral breast cancer	15 (5.2%)	15 (4.5%)
Ipsilateral breast cancer	0	2 (0.6%)
Endometrium cancer	5 (1.7%)	5 (1.5%)
Ovarian cancer [c]	0	1 (0.3%)
Leukemia	4 (1.4%)	1 (0.3%)
Acute myeloid leukemia	4 (1.4%)	0 [d]
Chronic lymphocytic leukemia	0	1 (0.3%)
Other	31 (10.8%)	29 (8.7%)
Lung	9 (3.1%)	4 (1.2%)
Gastrointestinal	7 (2.4%)	14 (4.2%)
Skin	3 (1.0%)	3 (0.9%)
Thyroid	3 (1.0%)	1 (0.3%)
Hematological [e]	2 (0.7%)	0
Kidney	2 (0.7%)	0
Bladder	1 (0.3%)	3 (0.9%)
Miscellaneous	4 (1.4%) [f]	4 (1.2%) [g]
Unknown [c]	1 (0.3%)	0
Death NED [h]	15 (5.2%)	16 (4.8%)

[a] First primary events are defined as breast cancer relapse, second primary malignancy, or death, whichever occurred first.

[b] Number of patients used in the calculation of percentages for primary events

[c] TAC Patient No [redacted] ad ovarian cancer, but was categorized as unknown because the type of SPM was not identified on the SPM page of the Case Report Form.

[d] FAC Patient No [redacted] was diagnosed with acute myeloid leukemia, but this was not considered a first primary event as it occurred after breast cancer relapse (see Table 4).

[e] Hematological malignancies include reports of myelodysplastic syndrome in TAC Patients No [redacted] . One additional patient (FAC Patient No [redacted]) had myelodysplastic syndrome reported as an SAE, but not as an efficacy event (see Table 20, Section 9.5.2).

[f] "Miscellaneous" includes one report each of uterine (Patient No [redacted] adrenal (Patient No. [redacted]), exocrine (salivary) (Patient N [redacted] and brain (Patient No [redacted] cancer.

[g] "Miscellaneous" includes one report each of breast (Patient N [redacted] cervical (Patient No. [redacted] anal vaginal (Patient No [redacted] cancer, as well as one cancer that was undetermined (Patient N [redacted]

[h] NED: no evidence of disease

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.
Adapted from PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs05_1evt_type.sas OUT=REPORT/OUTPUT/a6_dfs05_1evt_type_i.rtf (21JUN2010 - 19:41)

Breast cancer relapse was the most common DFS event in both groups (TAC: 216/287 events [75.3%]; FAC: 264/333 events [79.3%]) followed by SPMs (TAC: 56/287 events [19.5%]; FAC: 53/333 events [15.9%]). Overall, the frequency of SPMs reported as DFS events was similar in both treatment groups (TAC: 56; FAC: 53). Contralateral breast cancer was the most common of all SPMs (TAC: 15; FAC: 15); ipsilateral breast cancer

Page 23

was also reported (TAC: 0; FAC: 2). In addition to breast cancer, endometrial cancer (TAC: 5; FAC: 5), ovarian cancer (TAC: 1; FAC: 1), and leukemia (TAC: 4 [acute myeloid leukemia]; FAC: 1 [chronic lymphocytic leukemia]) were also reported. In addition, FAC Patient No[redacted] was diagnosed with acute myeloid leukemia, but this was not considered a first primary event as it occurred after breast cancer relapse (see Table 4).

Lung cancer was reported as a DFS event in both treatment groups (TAC: 9; FAC: 4). Additionally, lung cancer was also reported as an SPM in FAC Patient No.[redacted]because it occurred after breast cancer relapse (see Table 4). Information on the 14 patients with lung cancer is summarized as follows:

<u>TAC treatment group</u>

- Patient No[redacted]was a 52-year-old patient. Poorly differentiated nonsmall cell lung cancer was diagnosed 6.5 years after Cycle 1. Following a lobectomy of her left lung/left upper lobe with a complete resection of the lung cancer, the patient experienced a complete response (CR), and was alive with no evidence of disease 4.5 years after the diagnosis.
- Patient No.[redacted]was a 51-year-old patient. Nonsmall cell lung cancer was diagnosed 6.5 years after Cycle 1. The patient was treated with radiotherapy 2000 centi-Gray units (cGy) for 7 days at the sacrum, followed 20 days later by 1-day carboplatin/paclitaxel. The response was not evaluable (NE). She died 4 months later from “malignant disease other than breast cancer” (not otherwise specified).
- Patient No[redacted] was a 51-year-old patient. Basocellular skin carcinoma was diagnosed 4.5 years after Cycle 1; it was surgically excised and the patient experienced a CR. Squamous cell carcinoma of the lung was diagnosed 9.7 years after Cycle 1 of treatment. Anticancer therapy consisted of transplatin (TDDP), a transisomer of cisplatin (CDDP)/vinorelbine for 72 days. She died 9 months later from “malignant disease other than breast cancer” (not otherwise specified).
- Patient No.[redacted]was a 62-year-old patient with a history of chronic obstructive pulmonary disease. Small cell carcinoma of the lung was diagnosed 4.5 years after Cycle 1. The patient underwent wedge resection of the left upper lobe with lymph node dissection followed by 1-day etoposide/carboplatin as anticancer therapy. She died 4 years later from malignant disease other than breast cancer (not otherwise specified).
- Patient No[redacted] was a 54-year-old patient. Small cell carcinoma of the lung was diagnosed 8.4 years after Cycle 1. Anticancer therapy consisted of 1-day cisplatin/etoposide. She died 9 months later from “malignant disease other than breast cancer” (not otherwise specified).
- Patient No[redacted]was a 44-year-old patient. Squamous cell carcinoma of the lung was diagnosed 8.7 years after Cycle 1. Anticancer therapy consisted of 1-day carboplatin/gemcitabine. She died 7 months later from “malignant disease other than breast cancer” (not otherwise specified).
- Patient No.[redacted]was a 65-year-old patient. Poorly differentiated small cell carcinoma of the right lung was diagnosed 4.4 years after Cycle 1. Following anticancer therapy with 1-day carboplatin/etoposide, the response was NE, and she died 9 months later from a cause noted as “other”, specified only as “malignant disease”.

Page 24

- Patient No [redacted] was a 53-year-old patient. "Lung cancer" was diagnosed 5.9 years after Cycle 1; although the histological diagnosis was obtained, it was not further specified. Anticancer therapy consisted of 1-day carboplatin/gemcitabine, and the patient was alive 5 years after the diagnosis.
- Patient No [redacted] was a 57-year-old patient. "Lung cancer" was diagnosed 10.1 years after Cycle 1; although the histological diagnosis was obtained, it was not further specified. Following anticancer therapy with 4 cycles gemcitabine/carboplatin, the response was no change/stable disease (NC/SD), and the patient died 6 months later from "malignant disease other than breast cancer" (not otherwise specified).

FAC treatment group

- Patient No [redacted] was a 42-year-old patient. A diagnosis of "either nonoats cell lung cancer or renal cancer" was reported 7.7 years after Cycle 1, although no histopathological proof was reported. The patient was treated with gemcitabine/cisplatin (71 days), docetaxel (128 days), and erlotinib (11 days). The response was NC/SD, and the patient was alive 3.5 years after the unconfirmed diagnosis.
- Patient No [redacted] was a 48-year-old patient. Lung adenocarcinoma was diagnosed 3.5 years after Cycle 1. Following treatment with carboplatin/paclitaxel for 119 days, there was a partial response. She died 6 months later from "malignant disease other than breast cancer" (not otherwise specified).
- Patient No [redacted] was a 58-year-old patient. Lung adenocarcinoma was diagnosed 3.1 years after Cycle 1. The patient underwent an upper lobectomy, followed approximately 2.5 years later by paclitaxel/carboplatin therapy for approximately 8 months. Grade III invasive bladder cancer was reported approximately 2 years after the lung cancer, requiring a cystectomy. The response to all treatments was NC/SD, and the patient died 3 years later from "malignant disease other than breast cancer" (not otherwise specified).
- Patient No [redacted] was a 68-year-old patient. Nonsmall cell lung cancer, metastatic to the brain, was diagnosed 0.4 years after Cycle 1. Following radiotherapy 200 cGy (x 11 fractions) to the brain for 17 days, the response was NE. She died approximately 1 month later from "malignant disease other than breast cancer" (not otherwise specified).
- Patient No [redacted] was a 61-year-old patient. Small cell lung cancer was diagnosed 6.9 years after Cycle 1, and was not considered a DFS event because it occurred after breast cancer relapse approximately 5 years after Cycle 1. Treatment consisted of etoposide/cisplatin for 87 days and radiotherapy 4000 cGy for 24 days at the right upper lobe. She died approximately 1 year later from "malignant disease other than breast cancer" (not otherwise specified).

Overall, lung cancer as an SPM was reported in 14 patients (TAC: 9; FAC: 5). The duration of survival (ranging 3 to 5 year) in 3 TAC patients (Patients No. 11803, 20701, and 32312) and in 1 FAC patient (Patient No [redacted] suggests that the lung cancer was diagnosed and treated effectively. The roles of primary nonmetastatic breast cancer, irradiation, and prolonged survival are known to contribute independently to the risk of lung cancer, which is also influenced by

genetic, social, environmental, and lifestyle characteristics of the patients at risk. In this study, prolonged DFS might have been another contributing factor to the observed incidence of lung cancer.

The lack of key information (especially regarding medical history and risk factors), however, does not permit a meaningful interpretation of these second primary lung cancers. None of the lung cancers reported as an SPM was also reported as an SAE, and therefore additional information from safety reporting is not available.

Gastrointestinal malignancies were reported as SPMs in 21 patients (TAC: 7; FAC: 14).

Death without any evidence of disease was the first DFS event in 15 TAC and 16 FAC patients (5.0% of the total number of events).

There were 32 additional patients with SPMs (TAC: 15; FAC: 17) reported as efficacy events (but not as primary events since they occurred after either breast cancer relapse or another reported SPM) and they are summarized in Table 4.

Table 4 – Number of patients with other second primary malignancies occurring after a primary DFS event, by type of event – ITT population

	TAC (N=745)	FAC (N=746)
Number of patients with SPMs occurring after a DFS event	15	17
Contralateral breast cancer	3	5
Breast cancer	0	1
Ovarian cancer	1	0
Leukemia	0	1 [a]
Lung	0	1
Skin	10 [b]	6 [c]
Gallbladder	1	0
Bladder	0	1
Endometrium	0	1
Bone	0	1

[a] The type of leukemia reported for Patient No. [redacted] was acute myeloid leukemia.

[b] Two patients had 2 SPMs reported: Patient No. [redacted] skin tumor on the left shoulder and sternal skin) and Patient No [redacted] 2 nonmelanoma skin cancers).

[c] Two patients had 2 SPMs reported: Patient No. [redacted] 2 basal cell carcinomas) and Patient No. [redacted] (2 basal cell carcinomas).

DFS: disease-free survival, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, SPM: second primary malignancy, TAC: docetaxel, doxorubicin, and cyclophosphamide.

Adapted from Appendix 14.2.6.1.7.4.

The overall frequencies of SPMs reported after a primary DFS event were balanced between the 2 treatment groups (TAC: 15; FAC: 17). There were 2 patients (TAC: 1; FAC: 1) who had more than 1 SPM reported in addition to breast cancer, exclusive of patients with nonmelanoma skin cancers and DCIS. Patient No [redacted] TAC) had colon and gallbladder cancer, and Patient No [redacted] FAC) had lung and bladder cancer (see Appendix 14.2.6.1.7.4).

There were a total of 6 reports of leukemia: 5 acute myeloid leukemia (TAC: 4; FAC: 1) and 1 report of chronic lymphocytic leukemia (FAC). Five of the 6 cases of leukemia were primary

DFS events; one patient (Patient No. [redacted]) was diagnosed with leukemia after breast cancer relapse. Five of the 6 cases of leukemia were reported as TEAEs (see Section 9.5.2).

A formal histopathology report was missing in TAC Patients No. [redacted] (skin – basal cell carcinoma) and [redacted] (contralateral breast cancer), and for FAC Patients No. [redacted] (nonsmall cell lung cancer and possible renal cancer), [redacted] (planoepithelial cancer of the uterine cervix), [redacted] (bone), [redacted] (pancreas), an[redacted] gastrointestinal). Although these SPMs were not histologically confirmed, they were conservatively considered as efficacy events. Histological proof, although without the description of the specific histological cytotype, was obtained in FAC Patients No. [redacted] (malignant melanoma), [redacted] (malignant melanoma) [redacted] gastric cancer), and [redacted] (squamous cell cancer of the skin on the right hand, "superficially invasive").

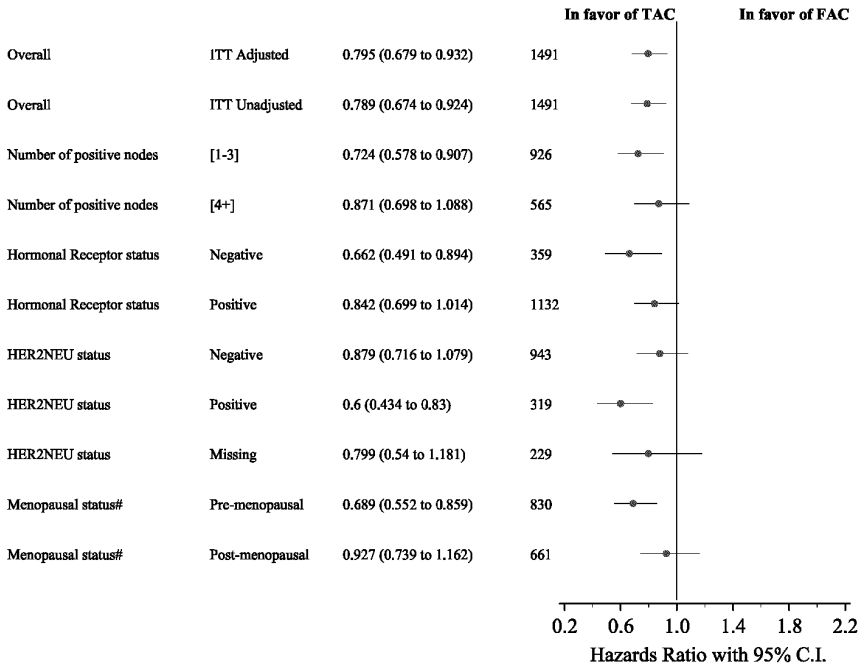
Second primary malignancies (SPMs) were reported in this study primarily as efficacy endpoints, either as the first primary DFS event (ie, an SPM that occurred prior to breast cancer relapse) or as an efficacy endpoint (ie, an SPM that occurred after the first primary DFS event [breast cancer relapse or an SPM]). In some instances, SPMs were also reported as serious adverse events (see Table 20 in Section 9.5.2 for SPMs reported as safety events). Of the SPMs reported as efficacy events, 109 SPMs were reported as DFS events (TAC: 56 [19.5%] events; FAC: 53 [15.9%] events) (Table 3). Of the 36 SPMs reported after a primary DFS event, 17 events occurred in 15 TAC patients and 19 events occurred in 17 FAC patients (Table 4). Therefore, a total of 145 SPM events (TAC: 73; FAC: 72) were reported as efficacy endpoints for 67 TAC patients and 66 FAC patients. These frequencies are substantially similar between the 2 treatment groups.

Information regarding first primary events and all DFS events are presented in Appendix 14.2.6.1.6 and Appendix 14.2.6.1.7, respectively. Confirmatory analyses are presented in Appendix 14.2.6.1.3 and Appendix 14.2.6.1.4.

Subgroup and interaction analysis

Figure 2 and Figure 3 are Forest plots presenting HRs and 95% CIs for DFS for TAC compared with FAC in certain subgroups.

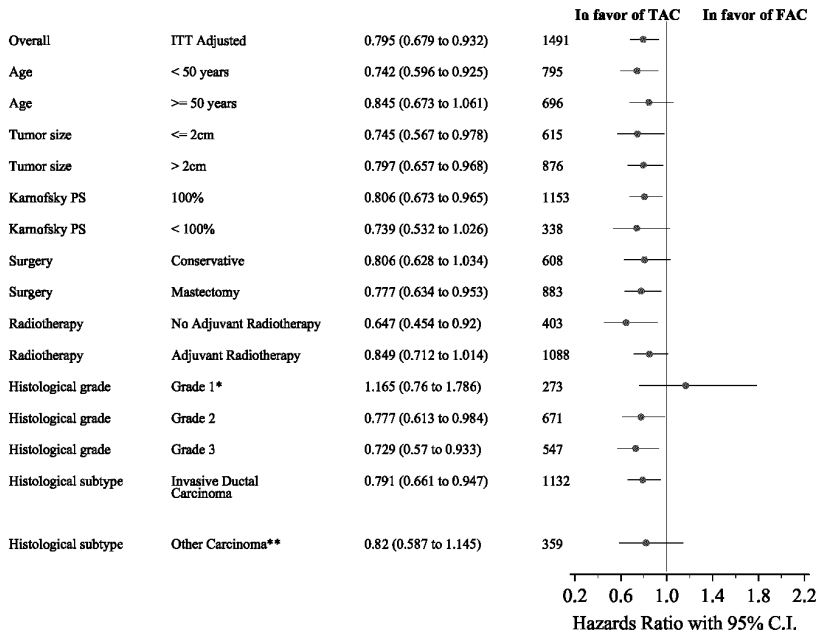
Figure 2 – Forest plot for disease-free survival, main subgroup analysis – ITT population



Premenopausal includes patients with status unknown but age < 50 years; postmenopausal includes patients with status unknown but age ≥50 years).
CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, HER2NEU: human epidermal growth factor receptor 2, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs_sub_main_fplt.sas OUT=REPORT/OUTPUT/a6_dfs_sub_main_fplt_i.rtf (21JUN2010 - 20:10)

Page 28

Figure 3 – Forest plot for disease-free survival subgroup analysis, other baseline characteristics – ITT population



* Grade 1 includes GX
** Other included Lobular, Classic or Variant Carcinoma
CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, GX: grade not assessed, ITT: intent-to-treat, PS: performance status, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_dfs_sub_bc_fplt.sas OUT=REPORT/OUTPUT/a6_dfs_sub_bc_fplt_i.rtf (21JUN2010 - 20:01)

Overall, the subgroup analyses (presented in Appendix 14.2.6.1.8) demonstrated a consistent benefit for TAC over FAC, and most of the unadjusted interaction analyses between treatment and each covariate did not show significant interactions (Appendix 14.2.6.1.12).

Few unadjusted interactions were below the significance threshold of 15%:

- Interaction term between treatment and menopausal status shows a p-value equal to 0.0557.
- Interaction term between treatment and HER2 status shows a p-value equal to 0.0903.
- Interaction term between treatment and hormonal receptor status shows a p-value equal to 0.1157.

However, these interactions appear to be quantitative and not qualitative since the related HR calculated within the subgroups still favors TAC (Figure 2 and Figure 3). This supports the consistency and robustness of the demonstrated benefit for TAC over FAC in the overall ITT population and across subgroups.

Sensitivity Analysis

A sensitivity analysis that censored nonbreast SPMs was conducted on DFS (Appendix 14.2.6.1.17.2). The results showed that the distribution of DFS was still significantly

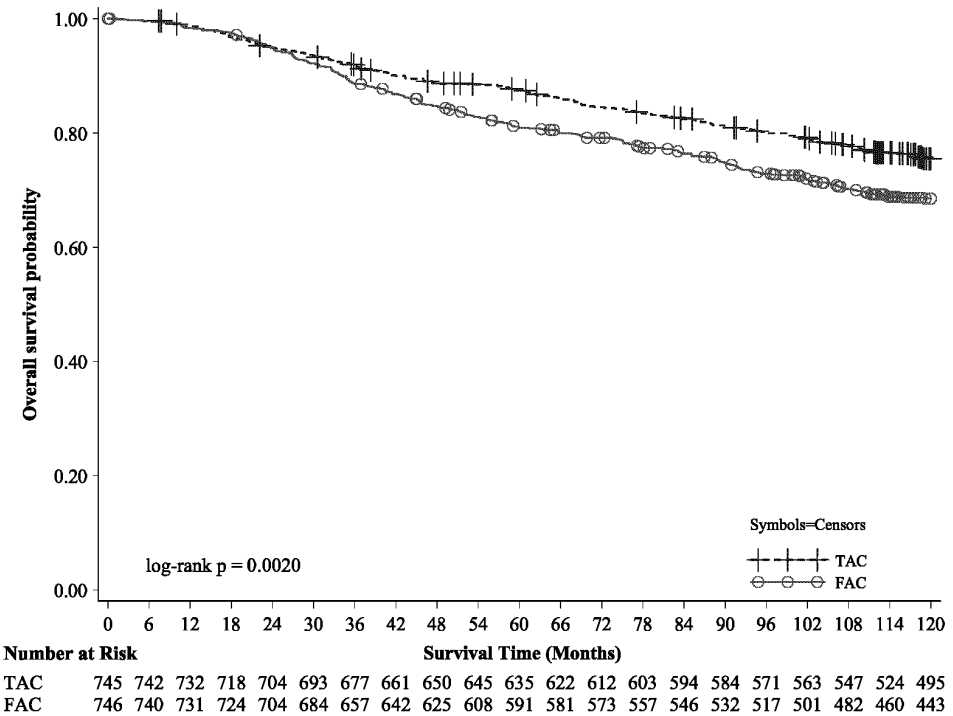
different between the 2 treatment groups and favored TAC (p = 0.0012; HR = 0.763 [CI: 0.647-0.899]).

8.2 OVERALL SURVIVAL ANALYSIS

At the cut-off date of 11 March 2010, there were a total of 429 deaths (TAC: 188; FAC: 241). Four (4) patients who died after their 10-year follow-up visit (TAC: Patient No. [redacted] FAC: Patients No [redacted] were not included in the OS analysis, but were included in the safety analysis.

TAC was associated with a 25.8% risk reduction in mortality compared to FAC (HR = 0.742, 95% CI: 0.613-0.898). The distribution of OS was significantly different between the 2 treatment groups using the log-rank test stratified on the number of axillary lymph nodes involved at randomization (log-rank p-value = 0.0020) (Figure 4 and Table 5).

Figure 4 – Overall survival – ITT analysis



FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_os_main_KMPlot.sas OUT=REPORT/OUTPUT/a6_os_main_KMPlot_i.rtf (21JUN2010 - 20:22)

Table 5 – Overall survival by axillary lymph nodes in all randomized patients, by randomization group – ITT analysis

Number of positive nodes	Statistics	TAC	FAC
All	Overall number assessed	745	746
	Overall number of events, n (%)	188 (25.2%)	241 (32.3%)
	Timepoint 36 months		
	Probability of surviving (95% CI) [a]	0.919 (0.899-0.939)	0.885 (0.863-0.908)
	Timepoint 60 months		
	Probability of surviving (95% CI) [a]	0.874 (0.850-0.898)	0.809 (0.781-0.838)
	Timepoint 120 months		
	Probability of surviving (95% CI) [a]	0.755 (0.724-0.786)	0.685 (0.651-0.719)
	Stratified log-rank test p-value [b]	0.0020	
	Adjusted Hazard ratio (95% CI) [c]	0.742 (0.613-0.898)	
1-3 Nodes	Overall number assessed	467	459
	Overall number of events, n (%)	79 (16.9%)	119 (25.9%)
	Timepoint 36 months		
	Probability of surviving (95% CI) [a]	0.955 (0.936-0.974)	0.910 (0.884-0.937)
	Timepoint 60 months		
	Probability of surviving (95% CI) [a]	0.929 (0.905-0.952)	0.853 (0.821-0.886)
	Timepoint 120 months		
	Probability of surviving (95% CI) [a]	0.841 (0.807-0.874)	0.751 (0.711-0.791)
	Unstratified log-rank test p-value	0.0008	
	Unadjusted Hazard ratio (95% CI)	0.616 (0.464-0.819)	
≥4 Nodes	Overall number assessed	278	287
	Overall number of events, n (%)	109 (39.2%)	122 (42.5%)
	Timepoint 36 months		
	Probability of surviving (95% CI) [a]	0.859 (0.818-0.900)	0.846 (0.804-0.888)
	Timepoint 60 months		
	Probability of surviving (95% CI) [a]	0.783 (0.734-0.832)	0.739 (0.687-0.790)
	Timepoint 120 months		
	Probability of surviving (95% CI) [a]	0.613 (0.555-0.671)	0.578 (0.519-0.636)
	Unstratified log-rank test p-value	0.2746	
	Unadjusted Hazard ratio (95% CI)	0.866 (0.668-1.122)	
Treatment by nodal status interaction	Unadjusted Interaction	1.407 (0.958-2.067) p=0.0814	

[a] Kaplan-Meier estimates

[b] Pairwise log-rank test stratified on the number of positive axillary nodes as per randomization

[c] Estimated using Cox proportional Hazard Model adjusted on the number of positive axillary nodes as per randomization.
CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.
Adapted from PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_os_main2.sas OUT=REPORT/OUTPUT/a6_os_main2_i.rtf (21JUN2010 - 20:12)
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_os_main_node2.sas OUT=REPORT/OUTPUT/a6_os_main_node2_i.rtf (21JUN2010 - 19:53)
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_os_int_posnod2.sas OUT=REPORT/OUTPUT/a6_os_int_posnod2_i.rtf (21JUN2010 - 20:07)

In the stratum "1 to 3 positive nodes", there were 79 and 119 deaths in TAC and FAC treatment groups, respectively. TAC was associated with a 38.4% risk reduction compared to FAC (HR = 0.616, 95% CI: 0.464-0.819). The difference was statistically significant (p = 0.0008).

In the stratum "4 and more positive nodes", there were 109 and 122 deaths in the TAC and FAC treatment groups, respectively. The risk reduction associated with TAC was not statistically significant (HR = 0.866, 95% CI: 0.668-1.122, p = 0.2746) in this subgroup.

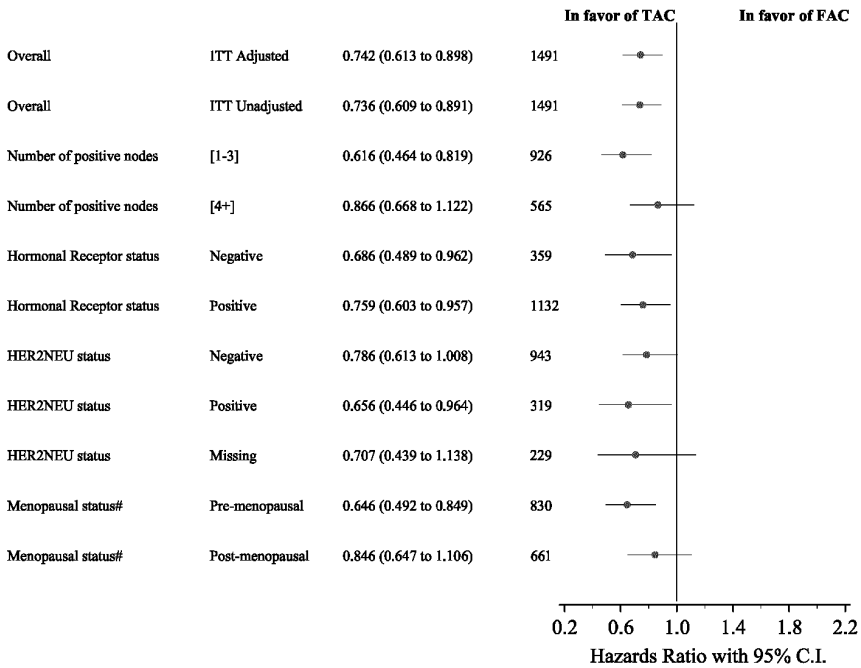
The treatment by nodal status interaction reached a significance level of p = 0.0814. This value was below the threshold of 0.15 defined in the SAP, indicating that there was some variability in the results of these 2 subgroups. However, the observed interaction seems to be more quantitative than qualitative in nature, because in both subgroups, the death rate was lower in TAC than in FAC; but, the treatment difference was greater in patients with 1 to 3 positive nodes (9.0% at 10 years) compared to 4+ positive nodes (3.5% at 10 years). The hazard ratio (HR = 0.866) for patients with 4+ positive nodes still favored TAC over FAC, but without reaching statistical significance.

Summaries of causes of death are shown in Appendix 14.2.6.2.6. Confirmatory analyses are presented in Appendix 14.2.6.2.3 to Appendix 14.2.6.2.5.

Subgroup and interaction analysis

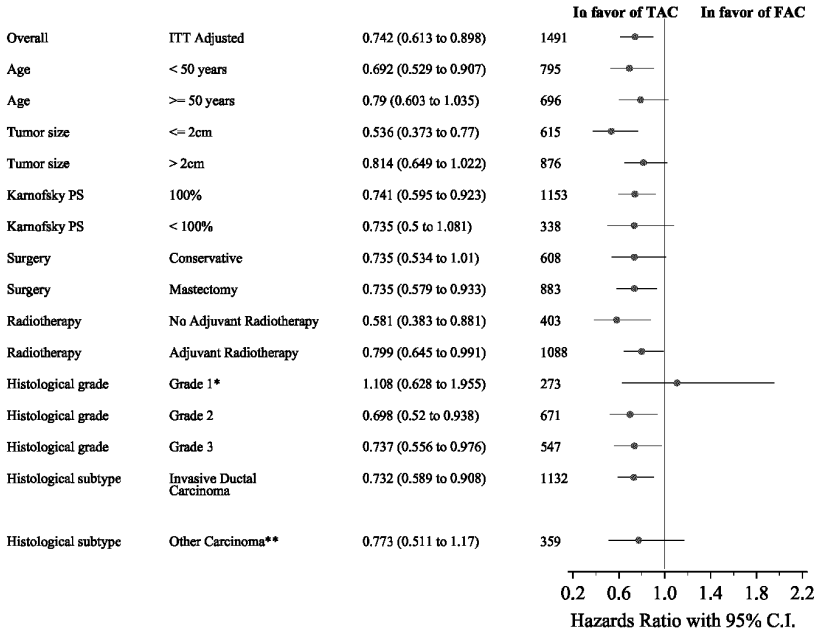
Figure 5 and Figure 6 are Forest plots presenting HRs and 95% CIs for OS for TAC compared with FAC in certain subgroups.

Figure 5 – Forest plot for overall survival, main subgroup analysis – ITT population



Premenopausal includes patients with status unknown but age < 50 years; postmenopausal includes patients with status unknown but age ≥50 years).
CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, HER2NEU: human epidermal growth factor receptor 2, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_os_sub_main_fplt.sas OUT=REPORT/OUTPUT/a6_os_sub_main_fplt_i.rtf (21JUN2010 - 19:38)

Figure 6 – Forest plot for overall survival subgroup analysis, other baseline characteristics – ITT population



* Grade 1 includes GX
** Other included lobular, classic or variant carcinoma
CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, GX: grade not assessed, ITT: intent-to-treat, PS: performance status, TAC: docetaxel, doxorubicin, and cyclophosphamide
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a6_os_sub_bc_fplt.sas OUT=REPORT/OUTPUT/a6_os_sub_bc_fplt_i.rtf (21JUN2010 - 19:47)

Overall, the subgroup analyses (presented in Appendix 14.2.6.2.9) demonstrated a consistent benefit for TAC over FAC, and most of the unadjusted interaction analyses between treatment and each covariate did not show significant interactions (Appendix 14.2.6.2.13).

Few unadjusted interactions were below the significance threshold of 15%:

- Interaction term between treatment and number of nodes shows a p-value equal to 0.0814.
- Interaction term between treatment and menopausal status shows a p-value equal to 0.1481.
- Interaction term between treatment and tumor size shows a p-value equal to 0.0575.

However, these interactions appear to be quantitative and not qualitative since the related HR calculated within the subgroups still favors TAC (Figure 5 and Figure 6). This supports the consistency and robustness of the demonstrated benefit for TAC over FAC in the overall ITT population and across subgroups.

Page 33

9 SAFETY EVALUATION

As discussed in Section 6.3.2, for this safety evaluation, "treatment period" is defined as the period from the date of randomization until 30 days after the last administration of study drugs. "Follow-up period" is defined as the period of time beginning after the end of the treatment period and ending at the completion of the 10-year follow-up period. The term "study period" refers to the entire study period, and includes both the treatment and follow-up periods. The focus of this safety evaluation is on the follow-up period because this includes new data beyond what has been presented in the interim study report at a median follow-up time of 55 months (dated 21 January 2004; Appendix 14.1.1).

9.1 EXTENT OF EXPOSURE

Of the 1491 randomized patients, 1480 patients were treated with study drugs (safety population: TAC: 744; FAC: 736). TAC was administered for 6 cycles at the planned doses to over 90% of randomized patients, and 4272 cycles of TAC were administered to 744 patients with 3940 cycles (92.2%) at the planned dose; 4348 cycles of FAC were administered to 736 patients, with 4269 cycles (98.2%) at the planned dose.

A full description of treatment exposure of patients in the TAX316 study is presented in the interim study report (Appendix 14.1.1, Section 8.1) and in Appendix 14.2.5.1.

9.2 POPULATION DEMOGRAPHICS

A full description of demographics for all patients in the TAX316 study is presented in the interim study report (Appendix 14.1.1, Section 6.3.1). Age and performance status of patients at baseline were comparable between treatment groups.

9.3 ADVERSE EVENTS

As discussed in Section 6.3.2, AEs were recoded into MedDRA. In addition, some conventions used in the interim study report (eg, adding laboratory safety parameters to the AE tables) were not repeated in this final report. Due to the changes in coding, the AE tables presented in this report do not exactly match those presented in the interim study report and subsequent safety update reports. The changes of the coding dictionary and of some of the editorial conventions adopted after the interim study report, however, do not substantially modify the overall safety conclusions regarding this study, particularly with regard to the analyses of the TEAEs occurring during the treatment period.

9.3.1 Summary of occurrence of adverse events

Table 6 summarizes the AEs, regardless of causality, reported during the treatment and follow-up periods. Adverse events occurring during the treatment period are considered TEAEs.

At least 1 TEAE was reported for almost all patients during the treatment period (TAC: 100%; FAC: 99.7%). More patients on TAC experienced at least one Grade 3 to 4 TEAE (TAC: 36.7%; FAC: 26.9%), serious TEAE (TAC: 35.9%; FAC: 9.1%), or serious Grade 3 to 4 TEAE (TAC: 10.1%; FAC: 4.9%). A TEAE was listed as a reason for discontinuing study medication for 45 (6.0%) TAC patients and for 8 (1.1%) FAC patients. There were 4 deaths during the treatment period (TAC: 2; FAC: 2), and 1 death in each treatment group was attributed to a TEAE related to study drugs (see Section 9.3.4.1 for further information on deaths).

In the follow-up period, the incidence of Grade 3 to 4 AEs (TAC: 13.8%; FAC: 11.3%) and SAEs (TAC: 7.1%; FAC: 4.5%) was higher in the TAC group, though the difference was not as great as that observed during the treatment period. There were 19 deaths (TAC: 8; FAC: 11) due to AEs reported during the follow-up period; of these, 3 deaths in the TAC group and 5 deaths in the FAC group were considered related to study drugs (see Section 9.3.4.1 for further information on deaths).

Table 6 – Overview of patients with adverse events regardless of causal relationship, by study period – safety population

	TAC (N=744)		FAC (N=736)	
	Treatment phase n (%)	Follow-up [a] n (%)	Treatment phase n (%)	Follow-up [a] n (%)
Patients with at least one AE	744 (100%)	523 (70.3%)	734 (99.7%)	495 (67.3%)
Patients with at least one G3-4 AE [b]	273 (36.7%)	103 (13.8%)	198 (26.9%)	83 (11.3%)
Patients with at least one serious AE (SAE)	267 (35.9%)	53 (7.1%)	67 (9.1%)	33 (4.5%)
Patients with at least one serious G3-4 AE (SAE) [b]	75 (10.1%)	42 (5.6%)	36 (4.9%)	32 (4.3%)
Patients discontinued due to AE	45 (6.0%)	0	8 (1.1%)	0
Patients with death due to AE [c]	2 (0.3%)	8 (1.1%)	2 (0.3%)	11 (1.5%)

[a] Nonserious follow-up AEs are those starting or worsening during follow-up. Serious follow-up AEs (SAEs) are those starting as or becoming serious during follow-up.

[b] Worst grade per patient, as reported by the Investigator.

[c] All deaths reported during follow-up are included in the follow-up period.

AE: adverse event, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, G3-4: Grade 3 to 4, SAE: serious adverse event, TAC: docetaxel, doxorubicin, and cyclophosphamide

PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_aeoverview.sas OUT=REPORT/OUTPUT/a7_aeoverview_i.rtf (21JUN2010 - 18:51)

9.3.2 Adverse events during treatment period

All patients in the TAX316 study had completed study treatment by October 1999, and all TEAEs occurring during the treatment period were reported previously in the interim study report (Appendix 14.1.1, Section 8.2.1.1). They are presented again in this report in Appendix 14.2.7, coded in MedDRA, version 12.1. Appendix 14.2.7.1.5 presents TEAEs occurring during the treatment period regardless of relationship by SOC, high level group term, high level term, and PT, by grade. Appendices 14.2.7.1.6 and 14.2.7.1.7 present TEAEs occurring during treatment regardless of relationship by PT and grade, on a per patient and cycle basis, respectively. Appendix 14.2.7.2.2 and Appendix 14.2.7.2.3 present related TEAEs occurring during treatment by SOC and PT, by grade, on a per patient and cycle basis, respectively. Appendix 14.2.7.2.4 and Appendix 14.2.7.2.5 present related TEAEs occurring during treatment by PT and grade, on a per

Page 35

patient and cycle basis, respectively. A listing of all related TEAEs during the entire study is presented in Appendix 14.2.7.2.6. These tables incorporate coding and other changes since the interim study report, which do not substantially modify the overall safety conclusions.

9.3.3 Adverse events during follow-up

Adverse events during the follow-up period include possibly or probably related TEAEs that persisted into the follow-up period and possibly or probably related AEs that started or worsened during the follow-up period. Worsening was defined as an increase of at least 1 grade in intensity. For AEs starting or worsening during the follow-up period, Investigators were asked to identify the most likely cause as study drugs, tamoxifen, radiotherapy, tumor, or other. Further ongoing evaluation included relevant noncancer-related signs and symptoms occurring after completion of chemotherapy (eg, congestive heart failure, toxicities related to tamoxifen and/or radiation therapy). These AEs were evaluated and data captured during protocol-defined, routine follow-up visits (every 3 months for the first 2 years; then every 6 months during Years 3, 4, and 5; then once a year during the subsequent 5 years). Therefore, it is not always possible to determine the precise duration of the AE for those AEs that were reported as resolved.

TEAEs persisting into follow-up

Table 7 displays TEAEs that were first documented during the treatment period (incidence ≥2% in the TAC group) and persisted into the follow-up period, regardless of causal relationship. Most TEAEs were to be followed into the follow-up period, based on a protocol-defined clinical decision (see Section 5.5.4 of the interim study report in Appendix 14.1.1).

In both treatment groups, the most common TEAEs persisting into the follow-up period were alopecia (TAC: 92.3%; FAC: 87.6%), asthenia (TAC: 31.7%; FAC: 24.5%), and amenorrhea (TAC: 27.2%; FAC: 17.0%). Amenorrhea was reported as persisting into the follow-up period in 198 of 420 (47.1%) premenopausal patients in the TAC group and in 119 of 403 (29.5%) premenopausal patients in the FAC group (Appendix 14.2.7.13.1). The types of TEAEs persisting at the start of the follow-up period were similar in both treatment groups, with a greater than 10% difference between the 2 treatment groups seen only for peripheral edema (TAC: 16.0%; FAC: 3.1%) and amenorrhea. Among TEAEs that persisted into the follow-up period in >1% of patients, the majority of events resolved; however, amenorrhea remained ongoing in 121 of 202 (59.9%) TAC patients and in 86 of 125 (68.8%) FAC patients, and lymphedema remained ongoing in 6 of 11 (54.5%) TAC patients and in 1 of 1 (100%) FAC patient. In addition, nausea, stomatitis, pain, hot flush, arthralgia, increased weight, and lethargy remained ongoing in >25% of patients who had persisting events (>1%) in either treatment group.

Table 7 – Number (%) of patients with TEAEs during the treatment period (incidence ≥2% in TAC) that persisted into the follow-up period, regardless of causal relationship – safety population

	TAC (N=744)				FAC (N=736)			
MedDRA PT	All n (%)	Persisting into follow-up n (%)	Resolved[a] n (%)	Ongoing[a] n (%)	All n (%)	Persisting into follow-up n (%)	Resolved[a] n (%)	Ongoing[a] n (%)
Alopecia	728 (97.8)	687 (92.3)	658 (95.8)	29 (4.2)	715 (97.1)	645 (87.6)	629 (97.5)	16 (2.5)
Nausea	599 (80.5)	35 (4.7)	25 (71.4)	10 (28.6)	648 (88.0)	25 (3.4)	24 (96.0)	1 (4.0)
Asthenia	592 (79.6)	236 (31.7)	207 (87.7)	29 (12.3)	513 (69.7)	180 (24.5)	164 (91.1)	16 (8.9)
Stomatitis	510 (68.5)	18 (2.4)	13 (72.2)	5 (27.8)	374 (50.8)	13 (1.8)	13 (100)	0
Vomiting	330 (44.4)	5 (0.7)	3 (60.0)	2 (40.0)	436 (59.2)	2 (0.3)	2 (100)	0
Infection[b]	324 (43.5)	19 (2.6)	17 (89.5)	2 (10.5)	306 (41.6)	14 (1.9)	14 (100)	0
Pain	313 (42.1)	31 (4.2)	21 (67.7)	10 (32.3)	264 (35.9)	21 (2.9)	20 (95.2)	1 (4.8)
Fever in absence of infection	273 (36.7)	2 (0.3)	1 (50.0)	1 (50.0)	61 (8.3)	0	0	0
Constipation	271 (36.4)	17 (2.3)	14 (82.4)	3 (17.6)	255 (34.6)	16 (2.2)	14 (87.5)	2 (12.5)
Diarrhoea	262 (35.2)	7 (0.9)	6 (85.7)	1 (14.3)	205 (27.9)	2 (0.3)	2 (100)	0
Oedema peripheral	250 (33.6)	119 (16.0)	100 (84.0)	19 (16.0)	92 (12.5)	23 (3.1)	19 (82.6)	4 (17.4)
Amenorrhoea	212 (28.5)	202 (27.2)	81 (40.1)	121 (59.9)	136 (18.5)	125 (17.0)	39 (31.2)	86 (68.8)
Menstruation irregular	211 (28.4)	55 (7.4)	50 (90.9)	5 (9.1)	165 (22.4)	71 (9.6)	60 (84.5)	11 (15.5)
Dysgeusia	206 (27.7)	57 (7.7)	53 (93.0)	4 (7.0)	112 (15.2)	22 (3.0)	19 (86.4)	3 (13.6)
Myalgia	199 (26.7)	30 (4.0)	24 (80.0)	6 (20.0)	73 (9.9)	6 (0.8)	6 (100)	0
Peripheral sensory neuropathy	185 (24.9)	84 (11.3)	74 (88.1)	10 (11.9)	70 (9.5)	15 (2.0)	13 (86.7)	2 (13.3)
Hot flush	184 (24.7)	129 (17.3)	91 (70.5)	38 (29.5)	147 (20.0)	109 (14.8)	66 (60.6)	43 (39.4)
Dyspepsia	179 (24.1)	18 (2.4)	15 (83.3)	3 (16.7)	132 (17.9)	11 (1.5)	10 (90.9)	1 (9.1)
Skin disorder	176 (23.7)	59 (7.9)	55 (93.2)	4 (6.8)	105 (14.3)	42 (5.7)	41 (97.6)	1 (2.4)
Decreased appetite	161 (21.6)	22 (3.0)	20 (90.9)	2 (9.1)	130 (17.7)	8 (1.1)	7 (87.5)	1 (12.5)
Pyrexia	156 (21.0)	4 (0.5)	3 (75.0)	1 (25.0)	88 (12.0)	2 (0.3)	2 (100)	0
Headache	154 (20.7)	11 (1.5)	9 (81.8)	2 (18.2)	169 (23.0)	5 (0.7)	5 (100)	0
Arthralgia	144 (19.4)	30 (4.0)	22 (73.3)	8 (26.7)	67 (9.1)	10 (1.4)	8 (80.0)	2 (20.0)
Nail disorder	135 (18.1)	106 (14.2)	102 (96.2)	4 (3.8)	103 (14.0)	79 (10.7)	73 (92.4)	6 (7.6)
Weight increased	131 (17.6)	89 (12.0)	56 (62.9)	33 (37.1)	108 (14.7)	61 (8.3)	36 (59.0)	25 (41.0)
Insomnia	122 (16.4)	26 (3.5)	22 (84.6)	4 (15.4)	83 (11.3)	17 (2.3)	16 (94.1)	1 (5.9)
Lung disorder	118 (15.9)	25 (3.4)	24 (96.0)	1 (4.0)	64 (8.7)	19 (2.6)	17 (89.5)	2 (10.5)
Cough	100 (13.4)	4 (0.5)	3 (75.0)	1 (25.0)	72 (9.8)	4 (0.5)	3 (75.0)	1 (25.0)
Injection site reaction	99 (13.3)	21 (2.8)	21 (100)	0	88 (12.0)	22 (3.0)	22 (100)	0
Lacrimation increased	87 (11.7)	22 (3.0)	22 (100)	0	52 (7.1)	8 (1.1)	8 (100)	0
Hypersensitivity	85 (11.4)	4 (0.5)	3 (75.0)	1 (25.0)	21 (2.9)	0	0	0
Affective disorder	83 (11.2)	15 (2.0)	12 (80.0)	3 (20.0)	77 (10.5)	15 (2.0)	12 (80.0)	3 (20.0)
Dizziness	63 (8.5)	4 (0.5)	3 (75.0)	1 (25.0)	50 (6.8)	2 (0.3)	2 (100)	0
Oropharyngeal pain	60 (8.1)	0	0	0	53 (7.2)	1 (0.1)	1 (100)	0
Haemorrhoids	57 (7.7)	1 (0.1)	0	1 (100)	35 (4.8)	2 (0.3)	2 (100)	0
Chills	53 (7.1)	2 (0.3)	0	2 (100)	29 (3.9)	1 (0.1)	1 (100)	0
Flushing	49 (6.6)	2 (0.3)	0	2 (100)	26 (3.5)	0	0	0
Abdominal pain upper	46 (6.2)	1 (0.1)	1 (100)	0	22 (3.0)	3 (0.4)	2 (66.7)	1 (33.3)
Arrhythmia	46 (6.2)	1 (0.1)	0	1 (100)	36 (4.9)	4 (0.5)	4 (100)	0
Nasopharyngitis	45 (6.0)	0	0	0	62 (8.4)	1 (0.1)	1 (100)	0
Rhinorrhoea	39 (5.2)	9 (1.2)	9 (100)	0	27 (3.7)	2 (0.3)	2 (100)	0
Dry mouth	36 (4.8)	10 (1.3)	10 (100)	0	43 (5.8)	12 (1.6)	12 (100)	0
Upper respiratory tract infection	36 (4.8)	0	0	0	54 (7.3)	1 (0.1)	1 (100)	0

	TAC (N=744)				FAC (N=736)			
MedDRA PT	All n (%)	Persisting into follow-up n (%)	Resolved[a] n (%)	Ongoing[a] n (%)	All n (%)	Persisting into follow-up n (%)	Resolved[a] n (%)	Ongoing[a] n (%)
Dry skin	32 (4.3)	17 (2.3)	17 (100)	0	36 (4.9)	11 (1.5)	11 (100)	0
Lymphoedema	32 (4.3)	11 (1.5)	5 (45.5)	6 (54.5)	8 (1.1)	1 (0.1)	0	1 (100)
Pharyngitis	31 (4.2)	0	0	0	21 (2.9)	0	0	0
Conjunctivitis	29 (3.9)	5 (0.7)	4 (80.0)	1 (20.0)	35 (4.8)	2 (0.3)	2 (100)	0
Abdominal pain	28 (3.8)	0	0	0	10 (1.4)	0	0	0
Anxiety	28 (3.8)	1 (0.1)	1 (100)	0	32 (4.3)	4 (0.5)	3 (75.0)	1 (25.0)
Weight decreased	28 (3.8)	13 (1.7)	11 (84.6)	2 (15.4)	22 (3.0)	5 (0.7)	4 (80.0)	1 (20.0)
Peripheral motor neuropathy	26 (3.5)	6 (0.8)	6 (100)	0	14 (1.9)	1 (0.1)	1 (100)	0
Influenza like illness	25 (3.4)	0	0	0	18 (2.4)	0	0	0
Oral candidiasis	23 (3.1)	2 (0.3)	1 (50.0)	1 (50.0)	8 (1.1)	1 (0.1)	1 (100)	0
Dry eye	22 (3.0)	7 (0.9)	7 (100)	0	19 (2.6)	8 (1.1)	8 (100)	0
Vulvovaginal mycotic infection	22 (3.0)	0	0	0	12 (1.6)	0	0	0
Oral herpes	21 (2.8)	2 (0.3)	2 (100)	0	21 (2.9)	1 (0.1)	1 (100)	0
Dyspnoea	20 (2.7)	7 (0.9)	3 (42.9)	4 (57.1)	8 (1.1)	2 (0.3)	2 (100)	0
Epistaxis	20 (2.7)	0	0	0	15 (2.0)	0	0	0
Fatigue	19 (2.6)	5 (0.7)	4 (80.0)	1 (20.0)	14 (1.9)	3 (0.4)	3 (100)	0
Depression	18 (2.4)	1 (0.1)	1 (100)	0	18 (2.4)	2 (0.3)	1 (50.0)	1 (50.0)
Dysphagia	18 (2.4)	0	0	0	5 (0.7)	0	0	0
Dysuria	18 (2.4)	0	0	0	14 (1.9)	0	0	0
Pain in extremity	18 (2.4)	2 (0.3)	2 (100)	0	14 (1.9)	2 (0.3)	2 (100)	0
Influenza	17 (2.3)	0	0	0	19 (2.6)	0	0	0
Sinusitis	16 (2.2)	0	0	0	19 (2.6)	0	0	0
Vision blurred	16 (2.2)	3 (0.4)	3 (100)	0	14 (1.9)	2 (0.3)	2 (100)	0
Erythema	15 (2.0)	0	0	0	12 (1.6)	2 (0.3)	2 (100)	0
Lethargy	15 (2.0)	10 (1.3)	7 (70.0)	3 (30.0)	20 (2.7)	11 (1.5)	9 (81.8)	2 (18.2)
Respiratory tract infection	15 (2.0)	1 (0.1)	1 (100)	0	6 (0.8)	1 (0.1)	1 (100)	0

[a] Percentages are calculated over the number of patients for each event during follow-up period.

[b] All adverse events mapped to the MedDRA SOC infections and infestations

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, MedDRA: Medical Dictionary for Regulatory Activities, PT: preferred term, SOC: system organ class, TAC: docetaxel, doxorubicin, and cyclophosphamide, TEAE: treatment-emergent adverse event.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_aept_fup.sas OUT=REPORT/OUTPUT/a7_aept_fup_i.rtf (21JUN2010 - 18:53)

For a summary of all patients with AEs during the treatment period (occurring in >1% of patients) that persisted into the follow-up period, see Appendix 14.2.7.1.9.

AEs starting or worsening during follow-up

Table 8 displays the AEs starting or worsening during follow-up, by causality (for AEs occurring in >1 patient [related to study drugs] in either treatment group). Overall, 523 (70.3%) patients in the TAC group and 495 (67.3%) patients in the FAC group had AEs that started or worsened in the follow-up period (Table 6). Except for peripheral sensory neuropathy related to study drugs, which was more frequent in the TAC group (TAC: 3.8%; FAC: 0.7%), both the types and incidence rates of AEs starting or worsening in the follow-up period were similar in both treatment groups.

Amenorrhea was reported as starting or worsening in the follow-up period in 78 of 420 (18.6%) premenopausal patients in the TAC group and in 97 of 403 (24.1%) premenopausal patients in the FAC group (Appendix 14.2.7.13.1). Delayed-onset amenorrhea was attributed to study drugs in 70 (16.7%) premenopausal patients in the TAC group and in 79 (19.6%) premenopausal patients in the FAC group (Appendix 14.2.7.13.2). Irregular menstruation was reported as starting or worsening in the follow-up period in 35 of 420 (8.3%) premenopausal patients in the TAC group and in 31 of 403 (7.7%) premenopausal patients in the FAC group (Appendix 14.2.7.13.1). Irregular menstruation was attributed to study drugs in 27 (6.4%) premenopausal patients in the TAC group and in 18 (4.5%) premenopausal patients in the FAC group (Appendix 14.2.7.13.2).

For a complete summary of all patients with AEs starting or worsening in the follow-up period, see Appendix 14.2.7.1.12.

Table 8 – Number (%) of patients with adverse events starting or worsening in follow-up, by causality (for adverse events related to study drugs in >1 patient in either treatment group) – safety population

	TAC (N=744)					FAC (N=736)				
MedDRA PT	Study drug n (%)	Tamoxifen n (%)	Radiotherapy n (%)	Tumor n (%)	Other n (%)	Study drug n (%)	Tamoxifen n (%)	Radiotherapy n (%)	Tumor n (%)	Other n (%)
Amenorrhoea	71 (9.5)	2 (0.3)	0	0	6 (0.8)	79 (10.7)	15 (2.0)	1 (0.1)	0	6 (0.8)
Peripheral sensory neuropathy	28 (3.8)	1 (0.1)	4 (0.5)	0	4 (0.5)	5 (0.7)	0	2 (0.3)	0	1 (0.1)
Menstruation irregular	27 (3.6)	7 (0.9)	0	0	2 (0.3)	18 (2.4)	12 (1.6)	0	0	1 (0.1)
Cardiac failure congestive	19 (2.6)	0	0	0	6 (0.8)	12 (1.6)	0	0	0	5 (0.7)
Hot flush	19 (2.6)	163 (21.9)	0	0	9 (1.2)	17 (2.3)	179 (24.3)	3 (0.4)	0	9 (1.2)
Asthenia	18 (2.4)	2 (0.3)	23 (3.1)	0	14 (1.9)	14 (1.9)	5 (0.7)	31 (4.2)	1 (0.1)	2 (0.3)
Cardiac disorder [a]	17 (2.3)	0	0	0	4 (0.5)	16 (2.2)	0	1 (0.1)	0	4 (0.5)
Alopecia	15 (2.0)	4 (0.5)	0	0	3 (0.4)	16 (2.2)	2 (0.3)	0	0	1 (0.1)
Arthralgia	11 (1.5)	2 (0.3)	0	0	8 (1.1)	6 (0.8)	0	2 (0.3)	0	4 (0.5)
Nail disorder	10 (1.3)	1 (0.1)	0	0	0	9 (1.2)	0	0	0	0
Dysgeusia	7 (0.9)	0	0	0	3 (0.4)	4 (0.5)	0	1 (0.1)	0	0
Weight increased	7 (0.9)	24 (3.2)	0	0	4 (0.5)	10 (1.4)	22 (3.0)	0	0	3 (0.4)
Oedema peripheral	5 (0.7)	5 (0.7)	25 (3.4)	0	7 (0.9)	3 (0.4)	6 (0.8)	9 (1.2)	0	6 (0.8)
Amnesia	3 (0.4)	5 (0.7)	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Arrhythmia	3 (0.4)	0	1 (0.1)	0	2 (0.3)	2 (0.3)	1 (0.1)	0	0	4 (0.5)
Cognitive disorder	3 (0.4)	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Dry mouth	3 (0.4)	2 (0.3)	0	0	0	5 (0.7)	0	0	0	0
Fatigue	3 (0.4)	1 (0.1)	3 (0.4)	1 (0.1)	3 (0.4)	2 (0.3)	2 (0.3)	1 (0.1)	0	2 (0.3)
Myalgia	3 (0.4)	3 (0.4)	0	0	2 (0.3)	1 (0.1)	1 (0.1)	2 (0.3)	0	1 (0.1)
Myocardial ischaemia	3 (0.4)	0	0	0	4 (0.5)	0	0	0	0	6 (0.8)
Parosmia	3 (0.4)	0	0	0	0	0	0	0	0	0
Acute myeloid leukaemia	2 (0.3)	0	0	0	0	1 (0.1)	0	0	0	0
Atrial fibrillation	2 (0.3)	0	0	0	2 (0.3)	0	0	0	0	2 (0.3)
Decreased appetite	2 (0.3)	0	2 (0.3)	0	0	0	0	0	0	0

	TAC (N=744)					FAC (N=736)				
MedDRA PT	Study drug n (%)	Tamoxifen n (%)	Radiotherapy n (%)	Tumor n (%)	Other n (%)	Study drug n (%)	Tamoxifen n (%)	Radiotherapy n (%)	Tumor n (%)	Other n (%)
Hypoaesthesia	2 (0.3)	0	0	0	0	0	0	1 (0.1)	0	2 (0.3)
Lung disorder	2 (0.3)	0	1 (0.1)	0	2 (0.3)	1 (0.1)	0	2 (0.3)	1 (0.1)	2 (0.3)
Peripheral motor neuropathy	2 (0.3)	0	0	0	0	0	0	0	0	0
Stomatitis	1 (0.1)	0	0	0	5 (0.7)	2 (0.3)	0	0	0	0
Dry eye	0	0	0	0	0	2 (0.3)	0	0	0	0
Vulvovaginal dryness	0	12 (1.6)	0	0	0	2 (0.3)	16 (2.2)	0	0	3 (0.4)

[a] The term "cardiac disorder" includes terms "cardiac function", "cardiac function BP", "cardiac dysfunction", and "cardiac function decreased LVEF", and includes some patients already counted under the term "cardiac failure congestive".
BP: blood pressure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, LVEF: left ventricular ejection fraction, PT: preferred term, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_aept_stwrs2.sas OUT=REPORT/OUTPUT/a7_aept_stwrs2_i.rtf (21JUN2010 - 18:28)

Table 9 displays the outcome of the AEs that started or worsened in the follow-up period in ≥0.5% of TAC patients, regardless of causal relationship. Among the AEs starting or worsening in ≥3% of patients in either treatment group, events that remained ongoing in greater than >50% of patients included amenorrhea (TAC: 58.2%; FAC: 50.5%), weight increased (TAC: 60.0%; FAC: 55.6%), cardiac failure congestive (TAC: 52.0%; FAC: 47.1%), lymphedema (TAC: 62.5%; FAC: 53.8%), and cardiac disorder (TAC: 60.9%; FAC: 66.7%).

Table 9 – Outcome in patients with adverse events starting or worsening in follow-up, regardless of causal relationship (incidence ≥0.5% in the TAC group) – safety population

	TAC (N=744)			FAC (N=736)		
	All	Resolved[a]	Ongoing[a]	All	Resolved[a]	Ongoing[a]
MedDRA PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hot flush	177 (23.8)	131 (74.0)	46 (26.0)	200 (27.2)	136 (68.0)	64 (32.0)
Skin disorder	151 (20.3)	146 (96.7)	5 (3.3)	157 (21.3)	151 (96.2)	6 (3.8)
Amenorrhoea	79 (10.6)	33 (41.8)	46 (58.2)	99 (13.5)	49 (49.5)	50 (50.5)
Asthenia	53 (7.1)	39 (73.6)	14 (26.4)	52 (7.1)	48 (92.3)	4 (7.7)
Skin hyperpigmentation	45 (6.0)	39 (86.7)	6 (13.3)	48 (6.5)	42 (87.5)	6 (12.5)
Oedema peripheral	40 (5.4)	32 (80.0)	8 (20.0)	22 (3.0)	16 (72.7)	6 (27.3)
Peripheral sensory neuropathy	37 (5.0)	29 (78.4)	8 (21.6)	8 (1.1)	8 (100)	0
Menstruation irregular	35 (4.7)	28 (80.0)	7 (20.0)	31 (4.2)	23 (74.2)	8 (25.8)
Weight increased	35 (4.7)	14 (40.0)	21 (60.0)	36 (4.9)	16 (44.4)	20 (55.6)
Nausea	30 (4.0)	19 (63.3)	11 (36.7)	14 (1.9)	14 (100)	0
Vaginal discharge	28 (3.8)	25 (89.3)	3 (10.7)	17 (2.3)	17 (100)	0
Cardiac failure congestive	25 (3.4)	12 (48.0)	13 (52.0)	17 (2.3)	9 (52.9)	8 (47.1)
Lymphoedema	24 (3.2)	9 (37.5)	15 (62.5)	13 (1.8)	6 (46.2)	7 (53.8)
Pain	24 (3.2)	15 (62.5)	9 (37.5)	31 (4.2)	28 (90.3)	3 (9.7)
Skin exfoliation	24 (3.2)	23 (95.8)	1 (4.2)	35 (4.8)	35 (100)	0
Cardiac disorder[b]	23 (3.1)	9 (39.1)	14 (60.9)	21 (2.9)	7 (33.3)	14 (66.7)
Erythema	23 (3.1)	21 (91.3)	2 (8.7)	17 (2.3)	16 (94.1)	1 (5.9)
Infection[c]	23 (3.1)	19 (82.6)	4 (17.4)	17 (2.3)	17 (100)	0
Radiation skin injury	23 (3.1)	19 (82.6)	4 (17.4)	34 (4.6)	26 (76.5)	8 (23.5)
Arthralgia	22 (3.0)	14 (63.6)	8 (36.4)	12 (1.6)	8 (66.7)	4 (33.3)
Vaginal haemorrhage	22 (3.0)	22 (100)	0	24 (3.3)	24 (100)	0
Alopecia	21 (2.8)	16 (76.2)	5 (23.8)	19 (2.6)	18 (94.7)	1 (5.3)
Headache	18 (2.4)	13 (72.2)	5 (27.8)	5 (0.7)	5 (100)	0
Skin hypertrophy	17 (2.3)	11 (64.7)	6 (35.3)	11 (1.5)	7 (63.6)	4 (36.4)
Pulmonary fibrosis	13 (1.7)	3 (23.1)	10 (76.9)	12 (1.6)	3 (25.0)	9 (75.0)
Telangiectasia	13 (1.7)	5 (38.5)	8 (61.5)	15 (2.0)	6 (40.0)	9 (60.0)
Breast fibrosis	12 (1.6)	9 (75.0)	3 (25.0)	12 (1.6)	8 (66.7)	4 (33.3)
Vulvovaginal dryness	12 (1.6)	10 (83.3)	2 (16.7)	21 (2.9)	13 (61.9)	8 (38.1)
Dry skin	11 (1.5)	11 (100)	0	10 (1.4)	10 (100)	0
Nail disorder	11 (1.5)	11 (100)	0	9 (1.2)	9 (100)	0
Dysgeusia	10 (1.3)	8 (80.0)	2 (20.0)	5 (0.7)	5 (100)	0
Fatigue	10 (1.3)	7 (70.0)	3 (30.0)	7 (1.0)	5 (71.4)	2 (28.6)
Bone pain	9 (1.2)	8 (88.9)	1 (11.1)	5 (0.7)	4 (80.0)	1 (20.0)
Dermatitis	9 (1.2)	9 (100)	0	11 (1.5)	11 (100)	0
Night sweats	9 (1.2)	8 (88.9)	1 (11.1)	7 (1.0)	7 (100)	0
Amnesia	8 (1.1)	6 (75.0)	2 (25.0)	2 (0.3)	1 (50.0)	1 (50.0)
Dyspnoea	8 (1.1)	2 (25.0)	6 (75.0)	7 (1.0)	4 (57.1)	3 (42.9)
Insomnia	8 (1.1)	6 (75.0)	2 (25.0)	7 (1.0)	6 (85.7)	1 (14.3)
Peau d'orange	8 (1.1)	7 (87.5)	1 (12.5)	4 (0.5)	4 (100)	0
Weight fluctuation	8 (1.1)	4 (50.0)	4 (50.0)	3 (0.4)	1 (33.3)	2 (66.7)
Hirsutism	7 (0.9)	6 (85.7)	1 (14.3)	0	0	0
Myalgia	7 (0.9)	6 (85.7)	1 (14.3)	5 (0.7)	5 (100)	0
Myocardial ischaemia	7 (0.9)	5 (71.4)	2 (28.6)	6 (0.8)	6 (100)	0

Page 42

	TAC (N=744)			FAC (N=736)		
MedDRA PT	All n (%)	Resolved[a] n (%)	Ongoing[a] n (%)	All n (%)	Resolved[a] n (%)	Ongoing[a] n (%)
Pruritus	7 (0.9)	7 (100)	0	4 (0.5)	3 (75.0)	1 (25.0)
Constipation	6 (0.8)	1 (16.7)	5 (83.3)	3 (0.4)	2 (66.7)	1 (33.3)
Cough	6 (0.8)	3 (50.0)	3 (50.0)	5 (0.7)	4 (80.0)	1 (20.0)
Diarrhoea	6 (0.8)	2 (33.3)	4 (66.7)	0	0	0
Endometrial hypertrophy	6 (0.8)	4 (66.7)	2 (33.3)	3 (0.4)	2 (66.7)	1 (33.3)
Metrorrhagia	6 (0.8)	6 (100)	0	7 (1.0)	7 (100)	0
Oedema	6 (0.8)	3 (50.0)	3 (50.0)	10 (1.4)	10 (100)	0
Stomatitis	6 (0.8)	1 (16.7)	5 (83.3)	2 (0.3)	2 (100)	0
Affective disorder	5 (0.7)	4 (80.0)	1 (20.0)	11 (1.5)	8 (72.7)	3 (27.3)
Arrhythmia	5 (0.7)	3 (60.0)	2 (40.0)	7 (1.0)	6 (85.7)	1 (14.3)
Breast inflammation	5 (0.7)	5 (100)	0	0	0	0
Breast oedema	5 (0.7)	5 (100)	0	12 (1.6)	9 (75.0)	3 (25.0)
Dizziness	5 (0.7)	4 (80.0)	1 (20.0)	5 (0.7)	4 (80.0)	1 (20.0)
Dry mouth	5 (0.7)	5 (100)	0	5 (0.7)	5 (100)	0
Dysphagia	5 (0.7)	5 (100)	0	6 (0.8)	6 (100)	0
Lung disorder	5 (0.7)	5 (100)	0	6 (0.8)	4 (66.7)	2 (33.3)
Oesophagitis	5 (0.7)	3 (60.0)	2 (40.0)	4 (0.5)	4 (100)	0
Radiation injury	5 (0.7)	2 (40.0)	3 (60.0)	8 (1.1)	3 (37.5)	5 (62.5)
Vomiting	5 (0.7)	2 (40.0)	3 (60.0)	2 (0.3)	2 (100)	0
Atrial fibrillation	4 (0.5)	1 (25.0)	3 (75.0)	2 (0.3)	2 (100)	0
Back pain	4 (0.5)	1 (25.0)	3 (75.0)	7 (1.0)	3 (42.9)	4 (57.1)
Breast pain	4 (0.5)	4 (100)	0	1 (0.1)	1 (100)	0
Breast swelling	4 (0.5)	3 (75.0)	1 (25.0)	1 (0.1)	1 (100)	0
Cognitive disorder	4 (0.5)	1 (25.0)	3 (75.0)	1 (0.1)	0	1 (100)
Decreased appetite	4 (0.5)	4 (100)	0	0	0	0
Deep vein thrombosis	4 (0.5)	4 (100)	0	1 (0.1)	1 (100)	0
Depression	4 (0.5)	4 (100)	0	6 (0.8)	6 (100)	0
Impaired healing	4 (0.5)	4 (100)	0	4 (0.5)	1 (25.0)	3 (75.0)
Lethargy	4 (0.5)	3 (75.0)	1 (25.0)	3 (0.4)	1 (33.3)	2 (66.7)
Musculoskeletal chest pain	4 (0.5)	3 (75.0)	1 (25.0)	4 (0.5)	2 (50.0)	2 (50.0)
Musculoskeletal pain	4 (0.5)	4 (100)	0	3 (0.4)	2 (66.7)	1 (33.3)
Ovarian cyst	4 (0.5)	3 (75.0)	1 (25.0)	1 (0.1)	1 (100)	0
Pain in extremity	4 (0.5)	3 (75.0)	1 (25.0)	2 (0.3)	2 (100)	0
Peripheral motor neuropathy	4 (0.5)	3 (75.0)	1 (25.0)	0	0	0
Phlebitis	4 (0.5)	4 (100)	0	2 (0.3)	2 (100)	0
Pulmonary embolism	4 (0.5)	4 (100)	0	3 (0.4)	3 (100)	0
Skin discolouration	4 (0.5)	4 (100)	0	5 (0.7)	4 (80.0)	1 (20.0)
Skin reaction	4 (0.5)	4 (100)	0	3 (0.4)	3 (100)	0

[a] Percentages are calculated over the number of patients for each event during follow-up period.

[b] The term "cardiac disorder" includes terms "cardiac function", "cardiac function BP", "cardiac dysfunction", and "cardiac function decreased LVEF", and includes some patients already counted under the term "cardiac failure congestive".

[c] All adverse events mapped to the MedDRA SOC term Infections and infestations

BP: blood pressure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, LVEF: left ventricular ejection fraction , MedDRA: Medical Dictionary for Regulatory Activities , PT: preferred term, SOC: system organ class, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_aefup_out.sas OUT=REPORT/OUTPUT/a7_aefup_out_i.rtf (21JUN2010 - 18:51)

For a complete summary of the outcomes for AEs that started or worsened in the follow-up period, see Appendix 14.2.7.1.11.

9.3.4 Deaths, serious adverse events, and other significant adverse events

Narratives were provided in the interim study report for each death, SAE, discontinuation, or other event determined to be of clinical importance (Appendix 14.1.1, Section 13). For this 10-year final report, new narratives were written for patients with serious cardiac events, SAEs, acute myeloid leukemia, SPMs reported as AEs, or death for reasons other than malignancy that occurred after the 55-month follow-up period described in the interim study report. Any newly reported events or updated information for narratives of patients previously reported in the interim study report are also included in this 10-year final report (Section 13.3.1: see Table 21 for a listing of patients with events that occurred in the follow-up period and are described in narratives presented in the interim clinical study report, and see Table 22 for those patients with events that occurred in the follow-up period and are described in new narratives presented with this final clinical study report).

9.3.4.1 Deaths

As of the cut-off date of 11 March 2010, among the 1480 treated patients, 189 (25.4%) TAC patients and 242 (32.9%) FAC patients had died. There were 2 additional deaths (Patients No. [redacted] both randomized to FAC) excluded from the safety population because the patients did not receive treatment. Table 10 summarizes all deaths reported either during treatment or follow-up periods by treatment received and by the reported cause of death.

Table 10 – Number (%) of all deaths occurring by cause of death during study period – safety population

	TAC (N=744)	FAC (N=736)
Alive	555 (74.6%)	494 (67.1%)
Death on study	189 (25.4%)	242 (32.9%)
Death ≤30 days after last study treatment	2 (0.3%)	2 (0.3%)
Toxic death due to study chemotherapy		
Septic	0	0
Nonseptic	1 (0.1%)	1 (0.1%)
Nontoxic death		
Death due to additional chemotherapy	0	0
Breast cancer	0	0
Malignant disease, other than breast cancer	0	0
Other	1 (0.1%)	1 (0.1%)
Death >30 days after last study treatment	185 (24.9%)	239 (32.5%)
Toxic death due to study chemotherapy		
Septic	0	0
Nonseptic	3 (0.4%)	4 (0.5%) [a]
Nontoxic death		
Death due to additional chemotherapy	1 (0.1%)	1 (0.1%)
Breast cancer	153 (20.6%)	203 (27.6%)
Malignant disease, other than breast cancer	12 (1.6%)	14 (1.9%)
Other	16 (2.2%)	17 (2.3%)
Death date missing	2 (0.3%)	1 (0.1%)
Toxic death due to study chemotherapy		
Septic	0	0
Nonseptic	0	0
Nontoxic death		
Death due to additional chemotherapy	0	0
Breast cancer	0	0
Malignant disease, other than breast cancer	0	0
Other	2 (0.3%)	1 (0.1%)

[a] Does not include Patient N[redacted] whose death was considered by the Investigator to be related to study drugs; this patient's death was reported as a second primary malignancy and not as nonseptic toxicity due to study chemotherapy.
FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_death.sas OUT=REPORT/OUTPUT/a7_death_i.rtf (21JUN2010 - 18:58)

In each treatment group, 2 patients died during the treatment period, 1 in each group from nonseptic toxicity due to study chemotherapy (TAC Patient No[redacted]eart arrest; FAC Patient No[redacted] pulmonary embolism), and 1 in each group from causes considered by the Investigator to be unrelated to study drugs (TAC Patient No. [redacted] pulmonary embolism; FAC Patient No[redacted] hypovolemic shock). Brief descriptions of these deaths are provided at the end of this section.

In the TAC treatment group, 185 (24.9%) patients died in the follow-up period. Among these, 153 died due to breast cancer. Among the remaining 32 deaths in the follow-up period, 3 were considered due to nonseptic toxicity from study chemotherapy (2 CHF [Patients No. [redacted] and [redacted]] and 1 acute myeloid leukemia [Patient No. [redacted]]), 1 due to toxicity from

additional chemotherapy received after completion of study treatment (Patient No.[redacted]), 12 due to malignant disease other than breast cancer, and 16 due to "other" causes.

In the FAC treatment group, 239 (32.5%) patients died in the follow-up period. Among these, 203 died because of breast cancer. Among the remaining 36 deaths in the follow-up period, 5 were considered related to study chemotherapy, including 4 due to nonseptic toxicity from study chemotherapy (3 CHF [Patients No[redacted]] and 1 ventricular fibrillation [Patient No[redacted]]) and 1 (Patient No[redacted]) categorized as due to malignant disease other than breast cancer (acute myeloid leukemia). Of the remaining deaths, 1 was due to toxicity from additional chemotherapy received after completion of study treatment (Patient No[redacted] 14 were due to malignant disease other than breast cancer (including Patient No.[redacted] noted above), and 17 due to "other" causes.

Table 11 provides further details on the patients who died in the follow-up period from causes other than breast cancer (TAC: 32; FAC: 36).

Page 46

Table 11 – Deaths due to causes other than breast cancer, occurring >30 days after last administration of study drugs, by causality – safety population

Treatment arm	Cause	Patient No.	MedDRA preferred term or verbatim term	Number of years from last cycle
TAC	Nonseptic toxicity due to study chemotherapy	[redacted]	Acute myeloid leukaemia*	3.6
			Cardiac failure congestive*	9.5
			Arrhythmia*	2.7
			Cardiac failure congestive*	
TAC	Other		Cause of death unknown	4.9
			Myocardial infarction*	1.5
			Cardiopathy	
			Pneumoniae	5.4
			Septic shock pneumonia associated to mechanic ventilation by pseudomonas aeruginosa	8.2
			Unknown	8.9
			Myelosuppression + liver failure	9.6
			Suicide	5.2
			Cardiac arrest*	1.9
			Cardiac arrest	
			Completed suicide*	0.1
			Drowning (suicide)	
			Cardiovascular event	8.6
			Unknown reason, metastatic disease could not be ruled out	2.7
			Unknown	5.2
			Cerebral haemorrhage*	0.6
			Intracerebral hemorrhage	
			Chronic obstructive pulmonary disease	7
			Suicide	1.8
			Malignant disease	4.8
TAC	Malignant disease, other than breast cancer		Not specified [c]	6.5
			Not specified [c]	3.1
			Not specified [c]	10.2
			Not specified [c]	9.8
			Not specified [c]	11.2
			Not specified [c]	8.1
			Not specified [c]	8.9
			Not specified [c]	3.1
			Not specified [c]	9
			Not specified [c]	11.1
			Not specified [c]	9.6
			Not specified [c]	10.3

Treatment arm	Cause	Patient No.	MedDRA preferred term or verbatim term	Number of years from last cycle
TAC	Toxicity due to chemotherapy after relapse	[redacted]	Septic shock*	2.6
FAC	Nonseptic toxicity due to study chemotherapy		Cardiac failure congestive*	2.4
			Cardiac failure congestive*	5.4
			Ventricular fibrillation*	2
			Cardiac failure congestive*	8.2
FAC	Other		Respiratory failure	10.8
			Vascular event	9.6
			Death due to malignant disease breast or colic cancer is unknown	6.5
			Unknown	7.6
			Jaundice*,	5.5
			Icterus of unknown cause	
			Unknown	7.3
			Colitis ischemic	9.9
			Atrial fibrillation*,	7.1
			Cardiac failure congestive*	
			Oesophageal varices haemorrhage*	
			Urosepsis*,	
			Hepatic encephalopathy following GI bleeding with concomitant cardiac disorders and sepsis	
			CVA (subarachnoid hemorrhage)	5
			Unknown	6.6
			Suicide	0.6
			Mesenteric thrombosis and septic shock	7.5
			Hypercalcaemia	3.5
			Cerebral ischaemia*,	7.2
			Brain ischemia (not related to the protocol treatment)	
			Acute respiratory failure*,	0.1
			Hepatic vein thrombosis*,	
			Hepatorenal failure*,	
			Portalvein thrombosis/hepatic failure	
			Coronary artery disease*,	8.3
			Coronary artery disease	
			Myocardial ischaemia*,	0.5
			Cardiac arrest	
FAC	Malignant disease, other than breast cancer		Not specified [c]	5.5
			Not specified [c]	8.6
			Not specified [c]	3.7
			Not specified [c]	7.8
			Not specified [c]	2.2

Treatment arm	Cause	Patient No.	MedDRA preferred term or verbatim term	Number of years from last cycle
			Not specified [c]	0.2
			Not specified [c]	7.6
			Not specified [c]	10.9
			Not specified [c]	3.9
			Acute myeloid leukaemia*	4
			Not specified [c]	9.8
			Not specified [c]	8.2
			Not specified [c]	7.1
			Not specified [c]	8.5
FAC	Toxicity due to chemotherapy after relapse			3.2

* MedDRA preferred term·

[a] The cases of acute myeloid leukemia for TAC Patient No. and FAC Patient No. were considered by the Investigators as related to study drugs, but 1 was reported as nonseptic toxicity due to study chemotherapy and the other reported as a second primary malignancy in the Case Report Form.

[b] The cause of death for Patient No as incorrectly reported on the Case Report Form as "other", and should have been reported as "malignant disease other than breast cancer".

[c] Type of malignancy was not specified on the death page of the Case Report Form. Patients with SPMs are accounted for and discussed in Sections 8.1 and 9.5.2.

CVA: cerebrovascular event, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, GI: gastrointestinal, MedDRA: Medical Dictionary for Regulatory Activities, SPM: second primary malignancy, TAC: docetaxel, doxorubicin, and cyclophosphamide.

PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_death_nonbcr30d_list.sas
OUT=REPORT/OUTPUT/a7_death_nonbcr30d_list_i.rtf (21JUN2010 - 19:15)

Following are brief narratives for 10 patients with deaths considered by the Investigators to be related to study drugs. All related deaths were reported as AEs and occurred in 1 patient in each treatment group during the treatment period (TAC: Patient No. FAC: Patient No. and in 3 TAC (Patients No) and 5 FAC patients (Patients No.) in the follow-up period:

TAC treatment group:

Treatment period:

- Patient No. was a 61-year-old patient with a history of hypertension (treated with medication) and unspecified arrhythmia, who experienced a syncopal episode on Day 5 of Cycle 2. An electrocardiogram (ECG) showed atrial flutter, which resolved spontaneously. Two weeks later, she experienced sudden dyspnea followed by cardiac arrest and death. A pulmonary embolism was suspected. Atrial flutter, dyspnea, and cardiac arrest were considered possibly related to study drugs.

Follow-up period:

- Patient No. was a 46-year-old patient who, after completing 6 cycles of treatment and experiencing a disease-free period of 20 months, was diagnosed with acute myeloid leukemia. She died from leukemia approximately 26.5 months later, with no

evidence of relapse of breast cancer. The acute myelogenous leukemia was considered probably related to study drugs.

- Patient No [redacted] was a 65 year-old-patient who completed 6 cycles of treatment and adjuvant irradiation of her left breast. Medical history was significant for hypertension, diabetes, and thyroidectomy. Within the first year after the end of chemotherapy, the patient was diagnosed with chronic multi-factorial CHF (ejection fraction [EF]: 25%) primarily attributed to doxorubicin (cumulative dose of 301.0 mg/m^2) and to lateral wall myocardial infarction. Total occlusion of the proximal circumflex coronary artery, and mild atherosclerosis had been documented. The EF value further declined to 11.9% at 6 years; the patient was regularly seen by a cardiologist, and cardiomegaly, Grade 4 CHF, and New York Heart Association Class-III symptoms, appeared to be overall medically managed. Eight years after the end of chemotherapy, acute and chronic renal failure with elevated liver enzymes were diagnosed. The patient progressively declined and finally succumbed to her severe CHF, longstanding hypertension, and cardiomyopathy at 9.5 years.
- Patient No. [redacted] was a 65-year-old patient with a history of hypertension. The cumulative dose of doxorubicin was 295 mg/m^2. Seven months after beginning study treatment, the patient was hospitalized with a 1-week history of increasing dyspnea, nonproductive cough, lethargy, and insomnia. A chest x-ray was consistent with CHF and an ECG suggested a possible myocardial infarction. Cardiac function remained stable and responsive to therapy (with an LVEF of 28%, compared with 54% at baseline) for 2 years, until the patient was hospitalized with refractory CHF and Grade 4 arrhythmias, which led to her death 2 months later. The CHF and arrhythmias were attributed to study drugs.

FAC treatment group:

Treatment period:

- Patient No [redacted] was a 59-year-old patient with a history of deep vein thrombosis who was hospitalized during Cycles 1 and 2 for fever and neutropenia. Whereas the fever resolved on Day 14 of Cycle 2, she experienced 3 episodes of hypotension, the last one resulting in cardiorespiratory arrest. An echocardiogram showed acute right ventricular dilatation consistent with massive pulmonary embolism, and the patient died a few minutes later; the pulmonary embolism was considered related to study drugs.

Follow-up period:

- Patient No. [redacted] was a 68-year-old patient who, during study treatment, was diagnosed with hypertension and hypercholesterolemia considered unrelated to study drugs. Left ventricular ejection fraction, measured at baseline and during Cycle 3, were 62% and 55%, respectively. She received 6 cycles of treatment, and radiotherapy to her left breast; the cumulative dose of doxorubicin was 300.06 mg/m^2. Approximately 20 months after the last study treatment, she was diagnosed with an infiltrating adenocarcinoma of the endometrium. Twenty-six months after the last study treatment, the patient was diagnosed with pleural effusion considered a consequence of CHF. Approximately 3 months later, she was hospitalized with ascites and symptoms of CHF, and died 3 days later from CHF considered possibly related to study drugs.

- Patient No. [redacted] was a 55-year-old patient who discontinued study treatment after Cycle 5 because of a hematological toxicity (delayed recovery, absolute neutrophil count 1.41 x 10^9/L). Treatment included adjuvant radiotherapy to the left breast, and the cumulative dose of doxorubicin was 229 mg/m^2. Five years and 9 months after starting study treatment, the patient was hospitalized with CHF and pulmonary embolism associated with profound dyspnea and severe biventricular dysfunction. Three weeks later, the patient was readmitted with cardiogenic shock, a Grade 4 decrease of LVEF (15%), and uncontrolled atrial fibrillation. After complications with liver and renal failure, the patient died 2 days later. The autopsy confirmed signs of cardiomyopathy consistent with anthracycline toxicity. The CHF was considered related to study drugs.
- Patient No. [redacted] was a 35-year-old patient who completed 6 cycles of treatment, and adjuvant radiotherapy to the left breast. The cumulative dose of doxorubicin was 301 mg/m^2. After a disease-free period of 21 months, distant relapse of breast cancer was detected in the lung and mediastinum. Further chemotherapy with 1 cycle of docetaxel followed by 4 cycles of vinorelbine + 5-fluorouracil was administered. The patient died approximately 5.5 months after her relapse because of ventricular fibrillation. The autopsy demonstrated myocardial fibrosis and chronic myocarditis, with pseudomembranous colitis. The hypokalemia resulting from the colitis may have contributed to the arrhythmia. The ventricular fibrillation was considered possibly related to study drugs.
- Patient No [redacted] was a 70-year-old patient with history of hypertension, ischemic heart disease, and diabetes mellitus, who also received adjuvant radiotherapy to the left breast; baseline LVEF was 60%. During a follow-up visit 7.7 years after completion of study treatment, the patient was diagnosed with CHF, which was treated medically. The patient died from CHF 14 months later. The Investigator considered the CHF probably related to study drugs.
- Patient No [redacted] was a 51-year-old patient who completed 6 cycles of treatment. The patient had 2 surgical procedures for basal cell carcinoma of her ear and forearm, 20 and 26 months after chemotherapy, respectively. Five weeks after her last surgery, she was diagnosed with contralateral breast cancer relapse, confirmed by histopathology. Further chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil was administered; 22 months later, and 1 month after chemotherapy with docetaxel was started, she was diagnosed with acute myeloid leukemia confirmed by bone marrow biopsy. The patient died from leukemia 16 days after the diagnosis, with no evidence of additional breast cancer relapse. The acute myeloid leukemia was considered related to study drugs.

Following are brief narratives for the 2 patients with deaths considered by the Investigator to be unrelated to study drugs and occurring during the treatment period:

- TAC Patient No. [redacted] was a 51-year-old patient with prior history of pulmonary embolism, asthma, and obesity, who died suddenly on Day 2 of Cycle 4. A postmortem examination revealed pulmonary embolism as the cause of death.
- FAC Patient No. [redacted] was a 56-year-old patient with a history of hypercholesterolemia who tolerated Cycles 1 to 3 without an SAE. On Day 6 of Cycle 4, she was hospitalized with loss of consciousness with subsequent left hemiplegia and was diagnosed with

thrombus of right subclavian artery/carotid sinus/carotid arteries and treated with heparin. Subsequently, she developed hypovolemic shock attributed to hemothorax occurring during pleural catheter placement and was unresponsive to transfusion; a surgical intervention was unsuccessful.

Patients with AEs that led to death

As identified in Table 6, there were 10 TAC patients (2 during the treatment period and 8 during the follow-up period) and 13 FAC patients (2 during the treatment period and 11 during the follow-up period) who had AEs that led to death. Of these, 4 AEs in the TAC treatment group and 6 AEs in the FAC treatment group were considered by the Investigator as related to study drugs. Brief narratives for these patients were provided previously in this section.

9.3.4.2 Serious adverse events

Table 12 provides an overview of the incidence of SAEs reported by treatment group and study period, regardless of causal relationship. Serious events occurring during the treatment period are considered treatment-emergent (serious TEAEs).

Table 12 – Overview of serious adverse events by study period, regardless of causal relationship – safety population

	TAC (N=744)		FAC (N=736)	
	Treatment period n (%)	Follow-up period [a] n (%)	Treatment period n (%)	Follow-up period [a] n (%)
Patients with at least one serious AE (SAE)	267 (35.9%)	53 (7.1%)	67 (9.1%)	33 (4.5%)
Patients with at least one G3-4 serious AE (SAE) [b]	75 (10.1%)	42 (5.6%)	36 (4.9%)	32 (4.3%)
Patients discontinued due to serious AE (SAE)	28 (3.8%)	0	7 (1.0%)	0
Patients with death due to serious AE (SAE) [c]	2 (0.3%)	8 (1.1%)	2 (0.3%)	11 (1.5%)

[a] Nonserious follow-up AEs are those starting or worsening during follow-up. Serious follow-up AEs (SAEs) are those starting as or becoming serious during follow-up.
[b] Worst grade per patient, as reported by the Investigator.
[c] All deaths reported during follow-up are included in the follow-up period.
AE: adverse event, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, G3-4: Grade 3 to 4, SAE: serious adverse event, TAC: docetaxel, doxorubicin, and cyclophosphamide
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_sae_overview.sas OUT=REPORT/OUTPUT/a7_sae_overview_i.rtf (21JUN2010 - 19:00)

During the treatment period, more TAC patients experienced serious TEAEs (35.9%) than did FAC patients (9.1%). There were also more Grade 3 to 4 serious TEAEs reported in the TAC group (10.1%) than in the FAC group (4.9%).

The incidence of serious TEAEs that occurred in more than 1 patient in either treatment group during the treatment period, by AE preferred term, are presented in Appendix 14.2.7.3.2. The most frequently reported serious TEAE during chemotherapy in both treatment groups was fever

Page 52

in absence of infection (TAC: 25.1%; FAC: 3.3%). The most frequently reported nonhematological serious TEAEs during chemotherapy in both treatment groups were infection (TAC: 7.9%; FAC: 3.0%), vomiting (TAC: 1.5%; FAC: 0.8%), and nausea (TAC: 1.1%; FAC: 0.4%). Other serious TEAEs occurred in less than 1% of patients in either treatment group.

Few SAEs were reported in the follow-up period. More TAC patients experienced SAEs (TAC: 7.1%; FAC: 4.5%). The number of Grade 3 to 4 SAEs was similar in the 2 groups (TAC: 5.6%; FAC: 4.3%).

The incidence of SAEs occurring in the follow-up period, by event term and causality assessment, are presented in Appendix 14.2.7.3.4. The most frequently reported SAE occurring in the follow-up period was CHF, reported by Investigators in 23 (3.1%) TAC patients and 16 (2.2%) FAC patients. There was 1 additional CHF case in the TAC treatment group (Patient No [redacted]) that was reported as nonserious by the Investigator, but reassessed as serious by the Sponsor. Leukemia was reported as an SAE in 3 TAC patients and 2 FAC patients. One TAC patient had an SAE of peripheral sensory neuropathy occurring in the follow-up period. Most of the SAEs were attributed either to study drugs or to "other" causes. Cardiovascular AEs and SPMs are presented in more detail in Section 9.5 (special safety).

9.3.4.3 Adverse events leading to withdrawal

Adverse events leading to withdrawal during the treatment period were previously discussed in the interim study report (Appendix 14.1.1, Section 8.2.3). The incidence of study withdrawal due to TEAEs experienced during the treatment period is presented in Appendix 14.2.7.4.1.

9.3.5 Analysis of adverse events by age and race

Analyses of TEAEs by age and race were previously discussed in the interim study report (Appendix 14.1.1,Section 8.2.4). Tables showing an overview of TEAEs and SAEs by age group are presented in Appendix 14.2.7.15.

9.4 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory evaluations during the treatment period were previously discussed in Section 8.2.5 of the interim study report (Appendix 14.1.1). Tables summarizing hematological and biochemical abnormalities are presented in Appendix 14.2.8.

9.5 SPECIAL SAFETY

9.5.1 Cardiovascular

Cardiovascular TEAEs during the treatment period

Cardiac TEAEs and hypertensive/hypotensive TEAEs (collectively included with the cardiac events) occurring during the treatment period are displayed in Table 13, in the order of decreasing frequency of incidence in the TAC treatment group. The protocol required that all reports of CHF ("cardiac function" Grade 3 to 4) were to be reported as serious.

Table 13 – Number (%) of patients with cardiac TEAEs during the treatment period, overall and by severity grading (worst grade reported), regardless of causal relationship – safety population

	TAC (N=744)				FAC (N=736)			
MedDRA PT[a]	All grades n (%)	Grade >=3 n (%)	Serious n (%)	Led to D/C[b] n (%)	All grades n (%)	Grade >=3 n (%)	Serious n (%)	Led to D/C[b] n (%)
Any event	99 (13.3%)	7 (0.9%)	4 (0.5%)	4 (0.5%)	60 (8.2%)	5 (0.7%)	3 (0.4%)	3 (0.4%)
Arrhythmia	46 (6.2%)	2 (0.3%)	0	0	36 (4.9%)	2 (0.3%)	2 (0.3%)	1 (0.1%)
Hypotension	14 (1.9%)	0	1 (0.1%)	0	6 (0.8%)	1 (0.1%)	0	0
Cardiac disorder [c]	13 (1.7%)	0	0	2 (0.3%)	4 (0.5%)	0	0	1 (0.1%)
Palpitations	12 (1.6%)	0	0	0	7 (1.0%)	0	0	0
Hypertension	7 (0.9%)	1 (0.1%)	0	0	3 (0.4%)	1 (0.1%)	0	0
Orthostatic hypotension	5 (0.7%)	0	1 (0.1%)	0	2 (0.3%)	0	0	0
Myocardial ischaemia	3 (0.4%)	3 (0.4%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0	0
Pericardial effusion	3 (0.4%)	0	0	0	1 (0.1%)	0	0	0
Tachycardia	3 (0.4%)	0	0	0	2 (0.3%)	0	0	0
Angina pectoris	1 (0.1%)	0	0	0	1 (0.1%)	0	0	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0	0	0	0	0
Cardiac arrest	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0	0	0	0
Cardiac failure congestive [d]	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Ventricular extrasystoles	1 (0.1%)	0	0	0	0	0	0	0
Sinus tachycardia	0	0	0	0	1 (0.1%)	0	0	0

[a] Worst AE grade reported

[b] D/C - Discontinuation of chemotherapy

[c] The term "cardiac disorder" includes the terms "cardiac function", "cardiac function BP", "cardiac dysfunction", and "cardiac function decreased LVEF", and includes some patients already counted under the term "cardiac failure congestive".

[d] CHF in TAC Patient No [redacted] was reported as nonserious by the Investigator, but reassessed by the Sponsor as serious.

D/C: discontinuation, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, MedDRA: Medical Dictionary for Regulatory Activities, PT: preferred term, TAC: docetaxel, doxorubicin, and cyclophosphamide, TEAE: treatment-emergent adverse event.

PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_cardiac1.sas OUT=REPORT/OUTPUT/a7_ae_cardiac1_i.rtf (21JUN2010 - 18:15)

Cardiac TEAEs, regardless of relationship to study drugs, were observed in 99 (13.3%) TAC patients and 60 (8.2%) FAC patients during the treatment period. Overall, cardiac TEAEs, regardless of relationship to study drugs, were reported more frequently in the TAC treatment group than in the FAC treatment group. The incidences of cardiac TEAEs that were Grade 3 to 4, serious, or led to discontinuation were low and similar in each arm. There was 1 CHF reported in each treatment group during the treatment period, and it led to discontinuation of chemotherapy in the patient in the FAC group.

Cardiovascular AEs starting or worsening during the follow-up period

Cardiac AEs and hypertensive/hypotensive AEs (collectively included with the cardiac events) starting or worsening during the follow-up period are displayed in Table 14, in the order of decreasing frequency of incidence in the TAC treatment group.

Table 14 – Number (%) of patients with cardiac TEAEs starting or worsening in the follow-up period, overall and by severity grading (worst grade reported), regardless of causal relationship – safety population

	TAC (N=744)			FAC (N=736)		
MedDRA PT [a]	**All grades n (%)**	**Grade >=3 n (%)**	**Serious n (%)**	**All grades n (%)**	**Grade >=3 n (%)**	**Serious n (%)**
Any event	61 (8.2%)	33 (4.4%)	28 (3.8%)	57 (7.7%)	28 (3.8%)	23 (3.1%)
Cardiac failure congestive [b]	25 (3.4%)	25 (3.4%)	22 (3.0%)	17 (2.3%)	17 (2.3%)	15 (2.0%)
Cardiac disorder [c]	23 (3.1%)	0	1 (0.1%)	21 (2.9%)	1 (0.1%)	1 (0.1%)
Myocardial ischaemia	7 (0.9%)	4 (0.5%)	3 (0.4%)	6 (0.8%)	5 (0.7%)	4 (0.5%)
Arrhythmia	5 (0.7%)	2 (0.3%)	2 (0.3%)	7 (1.0%)	3 (0.4%)	3 (0.4%)
Atrial fibrillation	4 (0.5%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
Cardiac arrest	2 (0.3%)	2 (0.3%)	2 (0.3%)	0	0	0
Hypertension	2 (0.3%)	1 (0.1%)	0	3 (0.4%)	2 (0.3%)	0
Myocardial infarction	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)
Ventricular dysfunction	2 (0.3%)	0	0	0	0	0
Cardiomegaly	1 (0.1%)	0	0	0	0	0
Cardiomyopathy	1 (0.1%)	0	0	1 (0.1%)	0	0
Congestive cardiomyopathy	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Mitral valve stenosis	1 (0.1%)	1 (0.1%)	0	0	0	0
Orthostatic hypotension	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0	0
Pericardial effusion	1 (0.1%)	0	0	2 (0.3%)	0	1 (0.1%)
Tachycardia	1 (0.1%)	0	0	1 (0.1%)	0	0
Arrhythmia supraventricular	0	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Bundle branch block right	0	0	0	1 (0.1%)	0	0
Cardiotoxicity	0	0	0	1 (0.1%)	0	0
Conduction disorder	0	0	0	1 (0.1%)	1 (0.1%)	0
Coronary artery disease	0	0	0	3 (0.4%)	2 (0.3%)	1 (0.1%)

MedDRA PT [a]	TAC (N=744) All grades n (%)	TAC (N=744) Grade >=3 n (%)	TAC (N=744) Serious n (%)	FAC (N=736) All grades n (%)	FAC (N=736) Grade >=3 n (%)	FAC (N=736) Serious n (%)
Hypotension	0	0	0	1 (0.1%)	0	0
Sick sinus syndrome	0	0	0	1 (0.1%)	1 (0.1%)	0
Ventricular fibrillation	0	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)

[a] Worst AE grade reported

[b] Includes 1 case of Grade 1 cardiac function (TAC Patient No. [redacted] and 2 cases of Grade 2 cardiac function (TAC Patient No. [redacted] and FAC Patient No. [redacted] incorrectly reported as Grade 3 cardiac function (CHF) by the Investigator.

[c] The term "cardiac disorder" includes the terms "cardiac function", "cardiac function BP", "cardiac dysfunction", and "cardiac function decreased LVEF", and includes some patients already counted under the term "cardiac failure congestive".

AE: adverse event, BP: blood pressure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, LVEF: left ventricular ejection fraction, MedDRA: Medical Dictionary for Regulatory Activities, PT: preferred term, TAC: docetaxel, doxorubicin, and cyclophosphamide.

PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_cardiac3_fup.sas OUT=REPORT/OUTPUT/a7_ae_cardiac3_fup_i.rtf (21JUN2010 - 19:06)

Cardiac AEs starting or worsening in the follow-up period, regardless of relationship to study drugs, were observed in 61 (8.2%) TAC patients and 57 (7.7%) FAC patients. Serious and Grade 3 to 4 cardiac events were infrequently reported, and similar between the 2 treatment groups. Congestive heart failure was higher in the TAC treatment group (TAC: 3.4%; FAC: 2.3%); long-term cardiac safety was analyzed separately and is discussed further in the following subsections.

Congestive heart failure

Table 15 summarizes patients with CHF AEs reported during the treatment and follow-up periods.

Table 15 – Number (%) of patients with congestive heart failure, during study period – safety population

	TAC (N=744)	FAC (N=736)
Cardiac failure congestive [a]	26 (3.5%)	17 (2.3%)
Grade 3 [a,b]	21 (2.8%)	14 (1.9%)
Grade 4 [b]	5 (0.7%)	3 (0.4%)
Serious cardiac failure congestive [c]	23 (3.1%)	16 (2.2%)
Cardiac failure congestive leading to death	2 (0.3%)	4 (0.5%)

[a] Includes 1 case of Grade 1 cardiac function (TAC Patient No. [redacted] and 2 cases of Grade 2 cardiac function (TAC Patient No. [redacted] and FAC Patient No. [redacted] incorrectly reported as Grade 3 cardiac function (CHF) by the Investigator.

[b] Worst AE grade reported

[c] There were 4 cases of CHF that were reported as nonserious by the Investigators; but 1 case (TAC Patient No. [redacted]) was reassessed as serious by the Sponsor, and 3 cases (TAC: Patients No. [redacted] FAC: Patient No. [redacted] were incorrectly reported as CHF (see footnote a).

AE: adverse event, CHF: congestive heart failure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide.

PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_chf.sas OUT=REPORT/OUTPUT/a7_ae_chf_i.rtf (21JUN2010 - 18:46)

In total, 26 TAC patients and 17 FAC patients were reported to have developed CHF at some point during the treatment or follow-up period. However, in 2 TAC patients (Patients No. [redacted] and [redacted] and 1 FAC patient (Patient No. [redacted] the CHF was reported incorrectly because these patients experienced either Grade 1 or 2 cardiac function events. Removing these patients from the total CHF cases resulted in 24 TAC and 16 FAC patients for which CHF actually occurred. Congestive heart failure was diagnosed before the completion of study treatment in 1 patient in each treatment group (both following Cycle 5), whereas CHF was a posttreatment-emergent event in the remaining 41 patients. The majority of patients with CHF had each received a cumulative dose of doxorubicin of ≤300 mg/m^2 (as per protocol) during the conduct of the study (TAC: 16; FAC: 9), whereas 10 TAC patients and 8 FAC patients received a cumulative dose of doxorubicin >300 mg/m^2. Of those patients receiving a cumulative dose of doxorubicin >300 mg/m^2, only 2 TAC patients (Patients No. [redacted] and 2 FAC patients (Patients No. [redacted] and [redacted]) received a cumulative dose >305 mg/m^2; 1 FAC patient (Patient No. [redacted]) received a cumulative dose >310 mg/m^2. Two TAC patients (Patients No. [redacted]) and 1 FAC patient (Patient No. [redacted]) received additional anthracycline therapy in the follow-up period (see patient narratives for further details: [redacted].

Congestive heart failure was reported as serious in 23 TAC patients and 16 FAC patients. There were 4 cases of CHF that were reported as nonserious by the Investigators, but 1 case (TAC: Patient No [redacted]) was reassessed as serious by the Sponsor, and 3 cases (TAC: Patients N[redacted] and [redacted] FAC: Patient No [redacted]) were actually Grade 1 or 2 cardiac function events that did not correspond to CHF.

Congestive heart failure led to death in 2 TAC and 4 FAC patients. Detailed information for the 6 patients who died from CHF is included in the patient narratives (TAC: Patients No. [redacted] and [redacted]; FAC: Patients No. [redacted]). Four of the 6 patients who died received a cumulative dose of doxorubicin >300 mg/m^2 (TAC: Patient No [redacted]; FAC: Patients No. [redacted]), and only 1 patient received a cumulative dose of doxorubicin >305 mg/m^2 (FAC: Patient No. [redacted]). In the TAC group, both patients who died from CHF were over 60 years of age, 1 of the patients (Patient No. [redacted]) had adjuvant radiotherapy to the left chest wall, and both patients had additional risk factors for CHF (eg, hypertension, diabetes, lateral wall myocardial infarction, and mitral regurgitation). In the FAC group, 3 of the 4 patients who died from CHF were over 60 years of age (Patients No. [redacted]), 3 patients had adjuvant radiotherapy to the left chest wall (Patients No. [redacted]), and 3 patients (Patients No [redacted]) had additional risk factors for CHF including a history of hypertension, alcoholic liver disease, and/or diabetes.

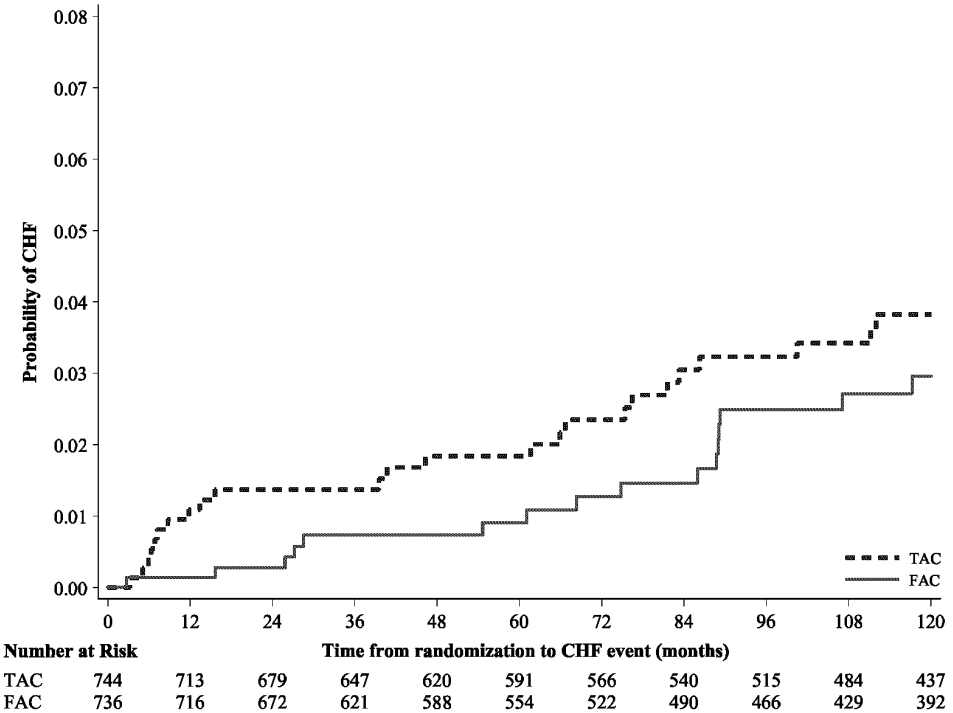
The cumulative incidence of CHF is shown in Table 16 and Figure 7. The difference in the incidence of CHF between the 2 treatment groups was not statistically significant. The Chi-square p-value comparing 26 CHF events reported in 744 patients for TAC and 17 CHF events reported in 736 patients for FAC is equal to 0.1748.

Table 16 – Cumulative incidence of congestive heart failure

	TAC (N=744)	FAC (N=736)
Number of CHF events [a]	26	17
55 months median follow-up	13 (50.0%)	5 (29.4%)
End of follow-up	13 (50.0%)	12 (70.6%)

[a] Number of patients used for the calculations
CHF: congestive heart failure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_chf_cuin2.sas OUT=REPORT/OUTPUT/a7_ae_chf_cuin2_i.rtf (21JUN2010 - 18:43)

Figure 7 – Cumulative incidence of congestive heart failure, time to cardiac event

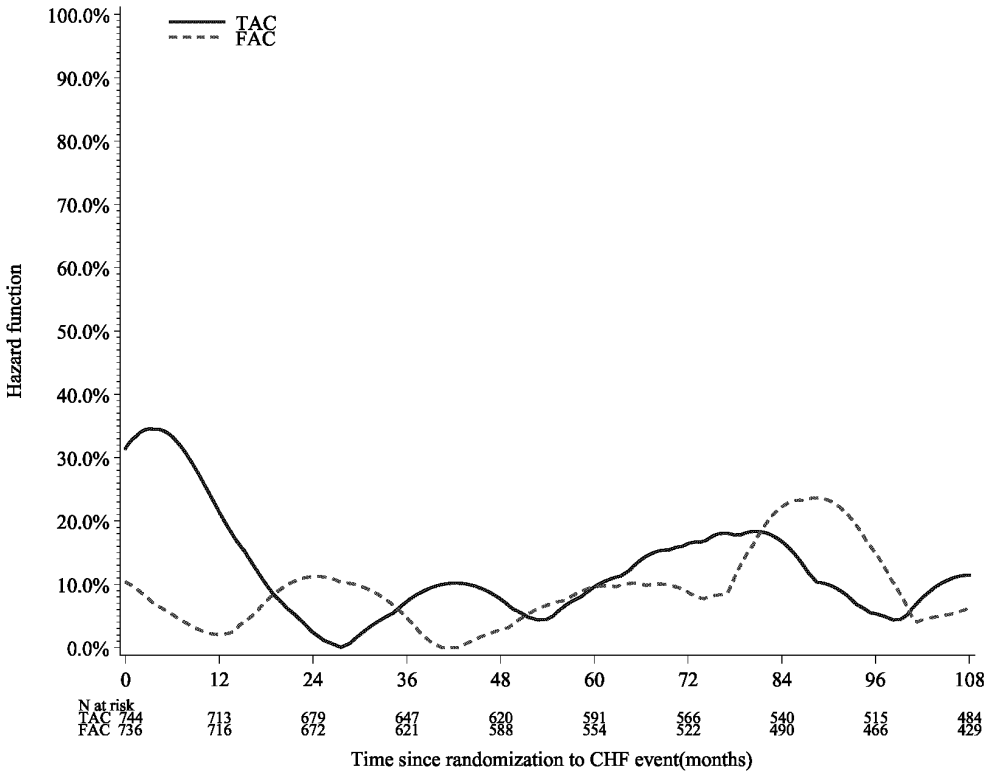


Number at Risk											
TAC	744	713	679	647	620	591	566	540	515	484	437
FAC	736	716	672	621	588	554	522	490	466	429	392

CHF: congestive heart failure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_chf_kmplt.sas OUT=REPORT/OUTPUT/a7_ae_chf_kmplt_i.rtf (21JUN2010 - 18:58)

The incidence of CHF plotted by hazard function is presented in Figure 8. The risk of CHF is higher in the TAC group in the first year, and from then on it is similar in both treatment groups. There is no higher cumulative or late occurrence of CHF in the TAC group compared with the FAC group.

Figure 8 – Incidence of congestive heart failure – hazard function (Kernel method)



CHF: congestive heart failure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_chf_hzrplt.sas OUT=REPORT/OUTPUT/a7_ae_chf_hzrplt_kr_i.rtf (21JUN2010 - 19:03)

The incidence of CHF was analyzed according to risk factors including age (≥65 years), weight (obesity defined with a body mass index ≥30), history of hypertension, diabetes, hypercholesterolemia, hyperlipidemia, cardiomyopathy, baseline LVEF, and previous radiation therapy in cardiac area (Table 17). Regarding risk factors such as hypercholesterolemia and hyperlipidemia, the available information was obtained from the medical history reported by the Investigators because no biological values (cholesterol and triglycerides) were to be collected systematically either at study entry or during the study period. Some of the more common risk factors observed in patients with CHF were age (≥65 years), obesity, hypertension, and irradiation of a left-side tumor.

Page 62

Table 17 – Risk factors for congestive heart failure during the study period – safety population

	Number of patients	TAC (N=744) CHF (N=26)	FAC (N=736) CHF (N=17)
Age			
<50	788	7 (26.9%)	5 (29.4%)
50-64	603	14 (53.8%)	7 (41.2%)
65+	89	5 (19.2%)	5 (29.4%)
Obesity (BMI>=30)			
Yes	369	9 (34.6%)	7 (41.2%)
No	1111	17 (65.4%)	10 (58.8%)
Hypertension			
Yes	246	14 (53.8%)	5 (29.4%)
No	1234	12 (46.2%)	12 (70.6%)
Diabetes			
Yes	36	4 (15.4%)	1 (5.9%)
No	1444	22 (84.6%)	16 (94.1%)
Hypercholesterolemia			
Yes	43	1 (3.8%)	0
No	1437	25 (96.2%)	17 (100%)
Hyperlipidemia			
Yes	9	0	0
No	1471	26 (100%)	17 (100%)
Cardiomyopathy			
Yes	1	0	0
No	1479	26 (100%)	17 (100%)
Baseline LVEF			
<50 or missing	78	1 (3.8%)	0
50-54%	126	2 (7.7%)	0
55-64%	605	7 (26.9%)	9 (52.9%)
65%+	671	16 (61.5%)	8 (47.1%)
Left-side tumor and radiation			
Yes	529	14 (53.8%)	7 (41.2%)
No	951	12 (46.2%)	10 (58.8%)

Risk factors defined as: age ≥ 65 years, diabetes, obesity (BMI >= 30), hypercholesterolemia, hyperlipidemia, left-sided radiation therapy, hypertension, and prior history of cardiomyopathy
BMI: body mass index, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, LVEF: left ventricular ejection fraction, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_chf_riskf.sas OUT=REPORT/OUTPUT/a7_ae_chf_riskf_i.rtf (21JUN2010 - 18:29)

Incidence of CHF and observation of at least 1 risk factor (age, diabetes, obesity, hypercholesterolemia, hyperlipidemia, left-side radiation therapy, hypertension, and prior history of cardiomyopathy) are summarized in Table 18. The percentage of patients with CHF that had no risk factors was similar in the TAC and FAC treatment groups (15.4% and 17.6%, respectively). Among the patients with at least 1 risk factor, approximately 60% did not develop CHF in either treatment group.

Table 18 – Congestive heart failure incidence and risk factors during the study period – safety population

	TAC (N=744)		FAC (N=736)	
	CHF (N=26)	No CHF (N=718)	CHF (N=17)	No CHF (N=719)
Number of patients without risk factors, N=595	4 (15.4%)	305 (42.5%)	3 (17.6%)	283 (39.4%)
Number of patients with at least 1 risk factor, N=885	22 (84.6%)	413 (57.5%)	14 (82.4%)	436 (60.6%)
Number of patients with 1 risk factor, N=553	6 (23.1%)	254 (35.4%)	9 (52.9%)	284 (39.5%)
Number of patients with 2 risk factors, N=244	10 (38.5%)	120 (16.7%)	1 (5.9%)	113 (15.7%)
Number of patients with at least 3 risk factors, N=88	6 (23.1%)	39 (5.4%)	4 (23.5%)	39 (5.4%)

Risk factors defined as: age ≥ 65 years, diabetes, obesity (BMI >= 30), hypercholesterolemia, hyperlipidemia, left-sided radiation therapy, hypertension, and prior history of cardiomyopathy
BMI: body mass index, CHF: congestive heart failure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_chf_incd.sas OUT=REPORT/OUTPUT/a7_ae_chf_incd_i.rtf (21JUN2010 - 18:00)

LVEF decrease comparisons

A total of 617 patients were evaluable for LVEF (ie, having 1 LVEF value at baseline and 1 LVEF value during the study period). Table 19 shows the relative decrease, and the decrease assessed versus the normal limit for the exam in the total population and in CHF patients. The percentage values were calculated based on the evaluable population.

Among all evaluable patients, 36.5% of patients in the TAC group and 29.7% of patients in the FAC group had no decrease in LVEF. Among all evaluable patients, 27.6% of patients in the TAC group and 29.4% of patients in the FAC group had a relative LVEF decrease between 0% and 10%. A 10% to 20% decrease in LVEF was reported in 19.3% of patients in the TAC group and in 25.7% of patients in the FAC group. A decrease of more than 20% in LVEF was reported in 16.7% of patients in the TAC group and in 15.2% of patients in the FAC group. Overall, the LVEF decreases among evaluable patients were similar in the 2 treatment groups, both in the total population and among CHF patients.

Table 19 – Number (%) of patients with relative decrease of LVEF, by evaluable patients, during study period – safety population

	TAC		FAC	
	All patients (N=744)	CHF patients (N=26)	All patients (N=736)	CHF patients (N=17)
Number of patients not evaluable	396 (53.2%)	10 (38.5%)	467 (63.5%)	6 (35.3%)
Number of patients evaluable	348 (46.8%)	16 (61.5%)	269 (36.5%)	11 (64.7%)
No LVEF decrease	127 (36.5%)	0	80 (29.7%)	0
LVEF decrease 0%-10%	96 (27.6%)	1 (6.3%)	79 (29.4%)	1 (9.1%)
Decrease within normal limits [a]	96 (27.6%)	1 (6.3%)	77 (28.6%)	1 (9.1%)
Decrease below lower normal limit	0	0	2 (0.7%)	0
LVEF decrease 10%-20%	67 (19.3%)	2 (12.5%)	69 (25.7%)	2 (18.2%)
Decrease within normal limits [a]	59 (17.0%)	1 (6.3%)	63 (23.4%)	2 (18.2%)
Decrease below lower normal limit	8 (2.3%)	1 (6.3%)	6 (2.2%)	0
LVEF decrease >20%	58 (16.7%)	13 (81.3%)	41 (15.2%)	8 (72.7%)
Decrease within normal limits [a]	25 (7.2%)	3 (18.8%)	22 (8.2%)	0
Decrease below lower normal limit	33 (9.5%)	10 (62.5%)	19 (7.1%)	8 (72.7%)

Note: Evaluable population is defined as patients with at least one LVEF measurement both at baseline and during study period.
Note: Percentage is based on evaluable patients.
[a] Lower normal limit replaced by 50% if normal limit was missing
CHF: congestive heart failure, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, LVEF: left ventricular ejection fraction, TAC: docetaxel, doxorubicin, and cyclophosphamide.
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_lvef_chf.sas OUT=REPORT/OUTPUT/a7_ae_lvef_chf_i.rtf (21JUN2010 - 18:52)
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_lvef.sas OUT=REPORT/OUTPUT/a7_ae_lvef_i.rtf (21JUN2010 - 19:06)

Among those evaluable patients not diagnosed with CHF and who had a relative decrease of LVEF >20%, the following cardiac conditions (most severe for each patient, described only once) were diagnosed:

- TAC: Grade 1 cardiac disorder (Patients No [redacted] Grade 2 cardiac disorder (Patients No [redacted]; Grade 1 arrhythmia (Patients No. [redacted] and [redacted]; Grade 3 arrhythmia (Patient No. [redacted]); Grade 2 tachycardia (Patient No. [redacted]; Grade 1 hypotension (Patient No. [redacted] and Grade 1 pericardial effusion (Patient No. [redacted]
- FAC: Grade 1 cardiac disorder (Patients No. [redacted] Grade 2 cardiac disorder (Patients No. [redacted] Grade 2 cardiomyopathy (Patient No [redacted]; Grade 1 arrhythmia (Patients No. [redacted]; and Grade 1 palpitations (Patients No. [redacted].

These cardiac conditions were all nonserious except for the Grade 3 arrhythmia in TAC Patient No. [redacted] .

For the evaluable patients not diagnosed with CHF, cardiac disorder includes the terms "cardiac function" and "cardiac function decreased LVEF".

9.5.2 Second primary malignancies

The occurrence of an SPM (defined in the protocol as histopathologically proven cancer, excluding nonmelanomatous skin cancer, in situ carcinoma of the cervix, and in situ carcinoma of the breast) was considered to be an efficacy event and is discussed in Section 8.1. Second primary malignancies were reported as primary efficacy endpoints (DFS events) if they occurred prior to breast cancer relapse; these SPMs reported as DFS events are summarized in Table 3, and are analyzed and discussed extensively in Section 8.1. As summarized in Section 8.1, a total of 67 patients in the TAC group had 73 SPMs, and 66 patients in the FAC group had 72 SPMs, reported as efficacy endpoints. These overall frequencies are substantially similar between the 2 treatment groups.

In addition to SPMs considered as efficacy endpoints, SPMs were reported as AEs in 6 TAC and 4 FAC patients (Table 20).

Page 66

Table 20 – Summary of second primary malignancies reported as adverse events

Treatment group	Patient No.	MedDRA PT	Diagnosis since last treatment (years)	Diagnostic method	Resulted in death?	Causality or most likely cause
TAC	[redacted]	Acute myeloid leukemia	4.1	Bone marrow aspirate & biopsy	No	Study drugs
		Acute myeloid leukemia	1.4	No histopathology reported [a]	Yes	Study drugs
		Basal cell carcinoma	0.2	Basal cell carcinoma	No	Other
		Myelodysplastic syndrome	1.9	No histopathology reported [b]	No	Other
		Refractory anemia with an excess of blasts	9.1	Pathology & cytogenentic reports	No	Study drugs
		Acute myelomonocyte leukemia	2.5	Bone marrow biopsy	No	Study drugs
FAC		Chronic lymphocytic leukemia	6.2	Peripheral blood smear	No	Other
		Acute myeloid leukemia	4.0	Smear bone marrow biopsy was negative (12-12-02)	Yes	Study drugs
		Myelodysplastic syndrome	8.4	Bone Marrow Biopsy	No	Study drugs
		Endometrial cancer	0.005 (2 days)	Endometrial Biopsy	No	None

[a] Histopathology for this event was not reported in the Case Report Form for this patient, but was later obtained through a data clarification form.

[b] Histopathology for this event was not reported on the SPM page of the Case Report Form, but was later obtained from the procedures page of the Case Report Form.

[c] The SPM for Patient No. [redacted] was classified as myelodysplastic syndrome in the DFS analysis.

DFS: disease-free survival, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, MedDRA: Medical Dictionary for Regulatory Activities, PT: preferred term, SPM: second primary malignancy, TAC: docetaxel, doxorubicin, and cyclophosphamide.

Adapted from PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_spm_teae.sas OUT=REPORT/OUTPUT/a7_ae_spm_teae_x.rtf (21JUN2010 - 18:45)
PGM=PRODOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_ae_spm.sas OUT=REPORT/OUTPUT/a7_ae_spm_x.rtf (06MAY2010 - 11:59)
PGM=DEVOPS/XRP6976D/TAX316/CSR/REPORT/PGM/a7_aelis.sas OUT=REPORT/OUTPUT/a7_aelis_x.rtf (14MAY2010 - 20:54)

Second primary malignancies reported as AEs were also considered efficacy events, except for those reported for FAC Patients No. [redacted] (which therefore are not included as primary DFS events):

- Patient No. [redacted] – This patient had myelodysplastic syndrome that was reported as an SAE; it was not assessed as an SPM, however, because the Investigator considered it a precancerous condition rather than a malignancy.

- Patient No. [redacted] - This patient had serious vaginal bleeding at baseline, which was later assessed as endometrial cancer. Because the vaginal bleeding was assumed to be present prior to enrollment, the endometrial cancer did not need to be reported as an SPM.

There were 2 patients (TAC: 1; FAC: 1) who had more than 1 SPM reported in addition to breast cancer, exclusive of patients with nonmelanoma skin cancers and DCIS (see Section 8.1).

After a follow-up of 10 years, there were 6 reports of leukemia: 5 acute myeloid leukemia (TAC: 4; FAC: 1), and 1 report of chronic lymphocytic leukemia (FAC). Five of the 6 cases of leukemia were reported as TEAEs. In addition, there were 3 reports of myelodysplastic syndrome (TAC: 2; FAC: 1).

Lung cancer was reported as a DFS event (TAC: 9; FAC: 4) and as an SPM that occurred after breast cancer relapse (TAC: 0; FAC: 1). None of the lung cancers reported as an SPM was also reported as an SAE, and therefore additional information from safety reporting is not available. An analysis of information on the patients with lung cancer is provided in Section 8.1.

Finally, there were 21 gastrointestinal SPMs reported as DFS events (TAC: 7; FAC: 14) (Section 8.1).

9.5.3 Other special safety

The incidence of febrile neutropenia and infection during the treatment period was previously discussed in the interim study report (Appendix 14.1.1, Section 8.2.6.1). Updated tables using MedDRA coding are presented in Appendix 14.2.7.6.

Adverse events related to fluid retention, gastrointestinal disorders, neurological disorders, respiratory disorders, and skin disorders that occurred during the treatment period were previously discussed in Sections 8.2.6.3, 8.2.6.4 , 8.2.6.5 , 8.2.6.7 , and 8.2.6.8 of the interim study report, respectively (Appendix 14.1.1). Updated summary tables and listings that use MedDRA coding are presented in Appendices 14.2.7.11, 14.2.7.8 , 14.2.7.9 , 14.2.7.10, and 14.2.7.12, respectively, for these areas of special safety concern.

9.6 SAFETY CONCLUSIONS

Docetaxel in combination with doxorubicin and cyclophosphamide (TAC) in the treatment of patients with operable node-positive breast cancer was associated with a safety profile that is consistent with the known toxicity of the individual drugs and the TAC combination.

Of the 1491 randomized patients in the study, 1480 patients were treated with study drugs. Almost all treated patients (>99%) experienced at least 1 TEAE during study treatment. Grade 3 to 4 TEAEs (TAC: 36.7%; FAC: 26.9%), serious TEAEs (TAC: 35.9%; FAC: 9.1%), and serious Grade 3 to 4 TEAEs (TAC: 10.1%; FAC: 4.9%) were reported more frequently in TAC patients during chemotherapy. Safety during the treatment period was previously reported in detail in the interim study report (see Section 8 of the interim study report, Appendix 14.1.1).

The focus of this 10-year final report is on the AEs during the follow-up period, for which new safety information is presented, as well as on the evaluation of cardiac toxicity and SPMs.

In the follow-up period, the incidence of Grade 3 to 4 AEs and SAEs was higher in the TAC group, though the difference was not as great as that observed during the treatment period.

The most common TEAEs persisting into the follow-up period in both treatment groups were alopecia (TAC: 92.3%; FAC: 87.6%), asthenia (TAC: 31.7%; FAC: 24.5%), and amenorrhea (TAC: 27.2%; FAC: 17.0%). Among TEAEs that persisted into the follow-up period in >1% of patients, the majority of events resolved; however, amenorrhea remained ongoing in 59.9% of TAC patients and 68.8% of FAC patients, and lymphedema remained ongoing in 6 of 11 (54.5%) TAC patients and in 1 of 1 (100%) FAC patient.

The types and incidence rates of AEs starting or worsening in the follow-up period were similar in both treatment groups, with the exception of peripheral sensory neuropathy (TAC: 3.8%; FAC: 0.7%), which was more frequently reported in the TAC group.

Serious adverse events occurred more frequently in TAC patients, both during the treatment period (TAC: 35.9%; FAC: 9.1%) and the follow-up period (TAC: 7.1%; FAC: 4.5%), although there were fewer events and less difference observed between the 2 groups during the follow-up period.

There were 10 fatal outcomes (TAC: 4; FAC: 6) that were considered related to study drugs. Two of these occurred during the treatment period, and 8 occurred in the follow-up period. The most common cause of treatment-related death occurring in the follow-up period was CHF (TAC: 2; FAC: 3).

In total, 26 patients in the TAC group and 17 patients in the FAC group were reported to have developed CHF at some point during the study period, with most cases reported in the follow-up period. The difference in the incidence of CHF between the 2 treatment groups was not statistically significant.

After a follow-up of 10 years, there were 6 reports of leukemia (TAC: 4; FAC: 2) and 14 patients with lung cancer. Lung cancer was reported both as a DFS event (TAC: 9; FAC: 4), and as an SPM that occurred after breast cancer relapse (TAC: 0; FAC: 1). Gastrointestinal SPMs were reported in a total of 21 patients (TAC: 7; FAC: 14).

In summary, this study demonstrated the safety profile of TAC compared with FAC when administered in a randomized trial to a population of women with operable, node-positive breast cancer. Although TAC was associated with a higher incidence of TEAEs and serious TEAEs than FAC during the treatment period, fewer events were reported in the follow-up period than on treatment, and the majority resolved. The higher incidence of AEs in the TAC group is not correlated with a higher incidence of fatal outcomes. The safety profile of TAC was predictable, manageable, and substantially consistent with previous controlled studies of adjuvant treatment with TAC, when compared to FAC. These safety findings should be interpreted in the context of significant improvement in DFS and OS among women with operable, node-positive breast cancer.

10 PHARMACOKINETIC EVALUATION

Not applicable

Page 70

11 DISCUSSION AND OVERALL CONCLUSIONS

This 10-year final analysis confirms the conclusions from the interim study report that there is a benefit of TAC over FAC as adjuvant treatment in women with operable, node-positive breast cancer.

The primary objective of this study was to compare DFS after treatment with TAC and FAC. The DFS analysis demonstrated that TAC was associated with a 20.5% relapse risk reduction compared with FAC. Additional subgroup analyses conducted for the predefined subgroups were consistent with the overall result showing superiority of TAC over FAC. Additional supportive analyses to assess the robustness of the results of the primary analysis confirmed the superiority of TAC over FAC. These results were consistent with the overall result showing superiority of TAC over FAC and strengthen the ability to generalize the results to a broadly defined population of women with operable, node-positive breast cancer.

A secondary objective of this study was to compare OS after treatment with TAC and FAC. The analysis of OS showed that TAC was associated with 25.8% risk reduction in mortality compared to FAC.

This demonstration of the additional efficacy advantage in both DFS and OS associated with the substitution of docetaxel for 5-fluorouracil, in combination with AC, is of clinical interest. The current efficacy results for TAC versus FAC are in favor of the docetaxel-based regimen. For both treatment groups, the DFS and OS curves are separate and in favor of TAC.

The safety profiles of TAC and FAC were predictable, manageable, and consistent with previous observations in breast cancer patients. There was a higher incidence of TEAEs and serious TEAEs in the treatment period among TAC patients compared to FAC patients. The types of TEAEs persisting at the start of the follow-up period were similar in both treatment groups, resolved in the majority of cases, and did not impact the frequency of fatal outcomes in the long term. After a follow-up of 10 years, the risk of leukemia and CHF with TAC is not greater than that described with anthracycline-based adjuvant chemotherapy programs (1, 2). Overall, SPMs occurred with a similar frequency in both treatment groups, with the exception of lung cancer being reported more frequently in the TAC group, and gastrointestinal malignancies being reported more frequently in the FAC group. The lack of information regarding medical history and risk factors, however, does not allow an interpretation of the observed incidence of second primary lung cancers.

In conclusion, the results from this study show that docetaxel in combination with doxorubicin and cyclophosphamide (TAC) offers an efficacy benefit to women with operable, node-positive breast cancer. In addition, the safety profile of TAC is consistent with the known toxicity of the individual drugs and of the TAC regimen. These results therefore indicate that TAC is an appropriate adjuvant chemotherapy option for women with operable, node-positive breast cancer.

12 REFERENCES

1. Pinder MC, Zhigang D, Goodwin JS, Nortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol. 2007;25(25):3808-15.
2. Diamandidou E, Buzdar AU, Smith TL, Frye D, Witjaksono M, Hortobagyi GN. Treatment-related leukemia in breast cancer patients treated with fluorouracil-doxorubicin-cyclophosphamide combination adjuvant chemotherapy: the University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol. 1996;14(10):2722-30.

13 SUPPORTIVE INFORMATION

13.1 DEMOGRAPHIC DATA

Not applicable

13.2 EFFICACY DATA

Not applicable

13.3 SAFETY DATA

13.3.1 Listing of narratives of deaths, serious adverse events, and other significant adverse events

Narratives were provided in the interim study report for each death, SAE, discontinuation, or other event determined to be of clinical importance (Appendix 14.1.1, Section 13). For this 10-year final report, new narratives were written for patients with serious cardiac events, SAEs, acute myeloid leukemia, SPMs reported as AEs, or death for reasons other than malignancy that occurred after the 55-month follow-up period described in the interim study report. Any newly reported events or updated information for narratives of patients previously reported in the interim study report (Appendix 14.4.1) are included in this 10-year final report in Table 21. Table 22 lists those patients with events occurring in the follow-up period described in new narratives presented with this final clinical study report.

Table 21 – Listing of patients with events in the follow-up period reported in the interim clinical study report narratives

Patient No.	SAE in follow-up reported in interim CSR	Grade	Follow-up information
TAC			
[redacted]	Myocardial infarction	4	None. Death due to MI reported in narrative
	Alopecia	2	Alive at 10 years, 7 mos (July 2008)
	Diverticulitis	4	None, as reported in narrative. Alive at 4 years, 3 mos.
	Fever in absence of infection Respiratory tract infection	2 3	Hospitalized for febrile neutropenia on 16 October 1998 and treated with antibiotics. Resolution date was not reported. On 15 November 1998 she was hospitalized for pneumonia and respiratory tract infection. She was treated with cefuroxime. The events resolved on 17 November 1998. These events were considered possibly related to study treatment. Died due to malignant disease January 2005. Survival 7 years, 1 mo.
	Peripheral sensory neuropathy Urinary retention	3 3	Alive 10 years, 6 mos. (November 2009)
	Peritonitis	4	Alive 10 years, 3 mos. (September 2009)
	Pulmonary embolism	2	Alive 11 years, 3 mos. (May 2009)
	Basel cell carcinoma	2	Died March 2008 due to malignant disease. Survival 10 years, 1 mo.
	Respiratory failure	3	On 16 April 2001, the patient was hospitalized for respiratory insufficiency. She was treated with albuterol and ipratropium. The event resolved on 20 April 2001. This event was considered unrelated to study treatment. Death from malignant disease reported in narrative.
	Pulmonary embolism	4	Alive 8 years, 10 mos. (May 2007)
	Cardiac arrest	4	None. Death from cardiac arrest reported in narrative.
	Complete suicide	4	None. Death reported in narrative.
	Pneumothorax	3	Alive 10 years, 3 mos. (June 2009) Pneumothorax mentioned in narrative but not in table at beginning of narrative.

[redacted]	Cerebral hemorrhage	4	None. Death from cerebral hemorrhage reported in narrative.
	Alopecia	1	Alive 10 years, 5 mos. (February 2010)
	Deep vein thrombosis	1	Alive 10 years, 6 mos. (March 2009)
	Acute myelomonocytic leukemia	4	None. Death from septic shock reported in narrative.
	Septic shock	4	
	Intestinal infarction	4	Died May 2003 from malignant disease.
	Pulmonary embolism	3	Survival 4 years, 8 mos.
	Cardiac failure congestive	3	
	Peritoneal infection	3	None. Death from malignant disease reported in narrative.
	Ventricular fibrillation	4	None. Death from ventricular fibrillation reported in narrative.
	Myocardial ischemia	3	Lost to follow-up May 2004. Survival 7 years, 2 mos.
	Myocardial ischemia	4	None. Death from malignant disease reported in narrative.
	Acute myeloid leukemia	4	None. Death from leukemia reported in narrative.
	Breast cancer SPM	--	Death due to breast cancer now believed to be only 1 SPM and not 2 as originally reported. The left breast focal adenocarcinoma in 2000 was another aspect of the invasive ductal carcinoma (first and only legitimate SPM) diagnosed in 1999 in the left breast.
	Pulmonary fibrosis	3	Alive 5 years, 3 mos. (January 2005)
	Acute respiratory failure	4	None. Death from hepatic failure reported in narrative.
	Dehydration	2	
	Hepatic vein thrombosis	4	
	Hepatorenal failure	4	
	Myocardial ischemia	4	None. Death reported in narrative.

CSR: clinical study report, MI: myocardial infarction, SAE: serious adverse event, SPM: second primary malignancy

Table 22 – Listing of patients with events in the follow-up period reported in the final clinical study report narratives

Patient number	Cardiac	SAE	Death during follow-up for reasons other than malignancy	Secondary primary malignancies reported as AEs
TAC				
[redacted]			X	
			X	
	X	X		
		X		X
	X	X		
	X	X		
	X	X		
	X	X		
		X		X
		X		
	X	X		
		X		
	X	X	X	
	X	X	X	
			X	
	X	X		
		X		
		X		
	X	X		
	X	X		
	X	X		
	X	X		
			X	
	X	X		
	X	X		
		X		
			X	
	X	X		
		X		
			X	

Patient number	Cardiac	SAE	Death during follow-up for reasons other than malignancy	Secondary primary malignancies reported as AEs
[redacted]		X		
	X	X		
	X	X		
	X	X		
	X	X	X	
	X	X	X	
		X		X
	X	X		
			X	
	X	X		
		X		X
	X	X		
	X	X		
		X		
	X	X		
	X	X	X	
			X	
	X	X		
	X	X		
	X	X		
	X	X		
	X	X	X	
			X	
		X		
			X	
		X	X	
			X	
	X	X		
	X	X		
	X	X		
	X	X		
			X	

Patient number	Cardiac	SAE	Death during follow-up for reasons other than malignancy	Secondary primary malignancies reported as AEs
[redacted]	X	X	X	
			X	
			X	
		X		
			X	
		X		X
	X	X		
	X	X	X	
	X	X		
	X	X		
	X	X		
		X		
	X	X		
	X	X	X	
		X		X
	X	X		
	X	X		

AE: adverse event, SAE: serious adverse event

13.4 PHARMACOKINETIC DATA

Not applicable

14 APPENDICES

See list of appendices.

Page 79

LIST OF APPENDICES

14 APPENDICES **79**

14.1 STUDY INFORMATION 82

14.1.1 TAX 316 published study report - 21 January 2004 83

14.1.2 Revisions to administrative appendices 36417
14.1.2.1 List of investigators who enrolled 36419
14.1.2.2 Study report author(s) 36500
14.1.2.3 Signature of principal investigator/sponsor's responsible medical officer 36502
14.1.2.4 Publications based on the study 36508
14.1.2.5 Important publications referenced in the report 36521

14.2 SUMMARY TABULATIONS AND PATIENT LISTINGS 36540

14.2.1 Patient disposition - See Appendix 14.1.1 (Appendix II) 36541

14.2.2 Protocol deviations - See Appendix 14.1.1 (Appendix II) 36542

14.2.3 Patients, visits, or observations excluded from efficacy analyses - See Appendix 14.1.1 (Appendix II) 36543

14.2.4 Demographic data, data at baseline and medications details - See Appendix 14.1.1 (Appendix II) 36544

14.2.5 Compliance and drug concentration data 36545
14.2.5.1 Compliance and dosing 36546

14.2.6 Efficacy Analysis 36551
14.2.6.1 Disease Free Survival 36556
14.2.6.2 Overall Survival 36697
14.2.6.3 Follow-up time (months) - Kaplan Meier Curve - Randomized population 36790
14.2.6.4 Follow-up time (months) - Randomized population 36791
14.2.6.5 Follow-up time (months) of lost to follow-up patients - Kaplan Meier Curve - Randomized population 36795
14.2.6.6 Follow-up time (months) of lost to follow-up patients - Randomized population 36796
14.2.6.7 Follow-up time (months) of lost to follow-up patients by treatment arm - Kaplan Meier Curve - Randomized population 36800
14.2.6.8 Follow-up time (months) of lost to follow-up patients by treatment arm - Randomized population 36801

14.2.7 Adverse event data 36805
14.2.7.1 All AEs 36810
14.2.7.2 All related AEs 37496
14.2.7.3 Serious AEs 41975
14.2.7.4 AEs leading to treatment discontinuation 42047
14.2.7.5 Deaths 42054
14.2.7.6 Neutropenia and Infection 42088
14.2.7.7 Cardiac disorders 42122
14.2.7.8 Gastric disorder 42473

14.2.7.9 Nerve disorder 43268
14.2.7.10 Respiratory disorder 43582
14.2.7.11 Fluid retention 43666
14.2.7.12 Skin disorder 43668
14.2.7.13 Amenorrhea 43677
14.2.7.14 Second Primary Malignancy 43679
14.2.7.15 TEAE by age group 43680
14.2.8 Clinical laboratory data 43695
14.2.8.1 Hematology 43697
14.2.8.2 Biochemistry 45587
14.2.9 Other safety observations - See Appendix 14.1.1 (Appendix II) 46912
14.3 CASE REPORT FORMS (CRFs) - Available upon request 46913
14.4 INDIVIDUAL PATIENT DATA LISTINGS 46914
14.4.1 Patient narratives 46915

BegDoc: Sanofi_00724262
EndDoc: Sanofi_00724342
BegAttach:
EndAttach:
PageCount: 81
Custodian: EMA
All Custodians:
Date Created: 06/18/2006
Date Last Modified: 12/01/2016
DocType: Document
Original FilePath:
FileName:
FileExt:
MD5 Hash: f5ec1edeee3874c753998b47b2d33f08
File Size: 926210
EMAIL Folder Path:
From:
To:
Subject:
Date Sent:
Date Received:
CC:
BCC:
Confidentiality: Confidential
Redacted: Yes
Embedded: False
Conversation Index Value:

EXHIBIT B

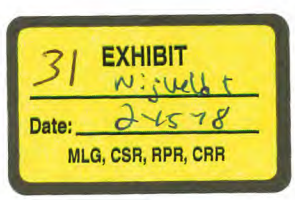
EXECUTIVE SUMMARY

SANOFI

Private & Confidential - Page 1 of 7 -

Inn / main brand	***DOCETAXEL*** ***Taxotere and Docetaxel Winthrop***
Formulation & dosage	*Two-vial formulation: Concentrate and Solvent for solution for infusion* 20 mg/0.5 ml and 80 mg/2 ml *One-vial formulation: Concentrate for solution for infusion* 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml
Topic	☐ Initial submission ☐ LCM: ☒ **Maintenance: safety-related** ☐ Other:
Labeling texts	☒ CCDS ☐ CCDM ☐ GLU ☐ CCSI ☒ USPI ☒ EUSPC ☐ JPI ☐ Other:
Source issue and Background and Summary of Recommendation	☒Internal: specify department: US-Legal ***Breast cancer, adjuvant setting:*** ***Update with TAX316 (node>0) and GEICAM (node <0) 10-year follow-up data*** **Background** **TAX316**: TAC (Taxotere-Doxorubicin-Cyclophosphamide) treatment in node positive patients with Breast cancer, adjuvant setting: • ***CCDS v26 (LRC 28-June-2011):*** *update with TAX316 10-year FU data: addition of persisting events* *(part of EU-FUM for above mentioned indication approved in 2004 to submit the 10-year FU CSR for TAX316)* • ***EU-SPC in line with CCDS v26:*** *PO 11Sept2011* • ***USPI: implementation plan approved by LRC at 28June2011 LRC meeting:*** ◦ ***Submission:*** *Postpone until FDA assessment of TAX316 CSR received.* ◦ ***Industrial implementation:*** *Postpone until FDA assessment of TAX316 CSR received* • ***Currently:*** *no information available on FDA feedback on TAX316 CSR.* • ***Presentation of USPI in line with CCDS v26 (June2011, TAX316 10-year follow-up data): LRC of 16Dec2016*** • **Privileged - Attorney-Client Communication** • ***LRC 16Mar2017: harmonization of CCDS/ EU-SPC/ USPI with TAX316 10-year FU data*** **Background** **GEICAM**: TAC (Taxotere-Doxorubicin-Cyclophosphamide) treatment in node negative patients with Breast cancer, adjuvant setting (with one or more high risk factors): • ***CCDS v29 (LRC 12-November-2014):*** *update with GEICAM 10-year FU data: addition of persisting events* *(Post-Authorization Measure in Europe to update the EU-SPC with GEICAM follow-up data at 8-10 years)*

{ FILENAME }



EXECUTIVE SUMMARY

SANOFI

Private & Confidential - Page 2 of 7 -

	• ***EU-SPC in line with CCDS v29:*** *PO 25Apr2014* • *USPI: Indication linked to GEICAM not approved in the US* • ***The LWG had the same approach for Labeling update with GEICAM FU update as for TAX316*** • ***LRC 16Mar2017: harmonization of CCDS/ EU-SPC with GEICAM 10-year FU data*** ☒ Internal: LWG proposes Docetaxel CCDS/ EU-SPC/ USPI update/ harmonization with persisting events, linked to TAX316 (update of the 3 Labeling documents) and GEICAM (CCDS/ EU-SPC update) 10-year follow-up data.
Objectives/Issues	☐ New Labeling Document Creation ☒ Update: CCDS/ EU-SPC/ USPI – Adverse events section *For Taxotere and docetaxel Winthrop EU-Labelings and US-Labelings*
LWG meeting dates	○ 16-Feb-2017 – 22-Feb-2017 – 3-Mar-2017
Participants	***Permanent*** / ***Ad Hoc***
	GRA Labeling: Vanina Groult / Global Statistics: Jeanne DEVIN
	GPE: Nanae Hangai (GSO) / US Legal: Harley RATLIFF - Jason STEINHART - Erin LESLIE
	GRA-US/Global: Sunil GUPTA GRA-EU: Christelle LAMORIL / US Advertising and Promotion: Marybeth TOSCANO
	Global Medical: Arvind SINGH, Ayse OZATILGAN / US Medical Oncology: Ted SZATROWSKI
Supportive Data/ Documentation (date and authors)	– **TAX316:** **CLINICAL STUDY REPORT**-Docetaxel-TAX316 (EFC6041/BCIRG001) 10-year follow-up- 09-Sep-2010 – **GEICAM:** **ABBREVIATED CLINICAL STUDY REPORT (FOLLOW-UP)-** Docetaxel-TAX.ES1.301/GEICAM 9805- 8-year and 10-year follow-up-02-Dec-2013 and **Appendix 14.2.7 Adverse event data**-02-Dec-2013
Safety Topics combined Y/N	– No
SMC decision date(s) per topic (if applicable)	– Not applicable
In case SMC to LRC >90 days add reason	

Outcome LWG	☒to LRC 16 March 2017 ☐no further action or update recommended

{ FILENAME }

EXECUTIVE SUMMARY

SANOFI

Private & Confidential

LRC	☐ LRC meeting 16 March 2017 ☒ LRC by circulation	*16-Mar-2017*
Summary of changes	**The following Labeling sections are proposed for update (for CCDS, EU-labeling and US-Labeling: harmonization):** Blue text added - red text deleted ***For Taxotere and docetaxel Winthrop EU-Labelings and US-Labelings:*** **11. ADVERSE REACTIONS** **11.1 Clinical Studies** **11.1.1 Combination therapy with *TM* in the adjuvant treatment of operable node–positive and high risk node negative breast cancer** **TAX316 10-year follow-up data – CCDS update** • **Acute Myeloid Leukemia (AML)/Myelodysplastic Syndrome** **After 10 years of follow up, in study TAX316, AML occurred in** 3 of 744 (0.4%) **patients who received *TM*, doxorubicin, and cyclophosphamide and in** 1 of 736 (0.1%) **patients who received fluorouracil, doxorubicin and cyclophosphamide. One TAC patient died due to AML during the follow up period (median follow-up time of 8 years). Myelodysplastic syndrome occurred in** 2 of 744 (0.3%) **patients who received *TM*, doxorubicin, and cyclophosphamide and in** 1 of 736 (0.1%) **patients who received fluorouracil, doxorubicin and cyclophosphamide.** • **Other persistent reactions** ~~**The most common adverse events persisting into the follow-up period in TAC patients were**~~ ~~**alopecia** (92.3%)**, asthenia** (31.7%)**, and amenorrhea** (27.2%)**. Among the adverse events that persisted into the follow-up period** in >1% of patients, the **majority of events resolved; however, amenorrhea** (59.9%)**, and lymphoedema** (54.5%)**) remained ongoing in TAC patients.**~~ **In Study TAX316, the most common adverse events persisting into the follow-up period in TAC patients** are described in below table **(median follow-up time of 8 years). Among the adverse events that persisted into the follow-up period the majority of events resolved.** **Table xx– Persistent reactions in patients receiving *TM* in combination with doxorubicin and cyclophosphamide. (TAX316)**

[redacted]

GEICAM 10-year follow-up data – CCDS update

- **Persistent reactions**

~~**The most common adverse events persisting into the follow-up period (median follow-up time of 10 years and 5 months) were alopecia** (49 patients, 9.2%), **amenorrhea** (18 patients, 3.4%) and **asthenia** (12 patients, 2.3%).~~

~~Among the adverse events that persisted into the follow-up period in >1% of patients, the majority of events resolved; however, amenorrhea (7 patients, 1.3%), peripheral sensory neuropathy (3 patients, 0.6%) and asthenia (2 patients, 0.4%) remained ongoing at the end of the follow-up period.~~

In Study GEICAM 9805, the most common adverse events persisting into the follow-up period in TAC patients are described in below table **(median follow-up time of 10 years and 5 months). Among the adverse events that persisted into the follow-up period the majority of events resolved.**

Table xx Persisting reactions in patients receiving *TM* in combination with doxorubicin and cyclophosphamide. (GEICAM 9805)

	***TM* 75 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² n = 532**	
	Persisting into the follow-up period N (%)	**Ongoing at the end of the follow-up period N (%)**
Alopecia*	49 (9.2)	3 (0.6)
Asthenia	12 (2.3)	2 (0.4)
Amenorrhea	18 (3.4)	7 (1.3)
Lymphoedema	5 (0.9)	4 (0.8)
Peripheral oedema	4 (0.8)	0 (0)
Peripheral sensory neuropathy	10 (1.9)	3 (0.6)

*** Alopecia** related to study drug **started or worsened during the follow-up period** in

42 patients (7.9%).

- **Cardiovascular events**

Three patients (0.6%) developed congestive heart failure during the follow-up period. At the end of the follow-up period (median follow-up time of 10 years and 5 months), no patients had CHF in TAC arm and **~~One~~ 1 patient died because of dilated cardiomyopathy.**

EU-SPC and USPI updates are in line with CCDS update.

LRC decision
16 March 2017

☐ Approved without change
☒ Approved with changes *specify: changes are highlighted in yellow*

TAX316:

Acute Myeloid Leukemia (AML)/Myelodysplastic Syndrome
After 10 years of follow up, in study TAX316, …

Other persistent reactions
In Study TAX316, the most common adverse events that started during the treatment period and persisted persisting into the follow-up period in TAC patients are described in below the table 12 **(median follow-up time of 8 years).** ~~**Among the adverse events that persisted into the follow-up period**~~
The majority of the events that had persisted resolved during the follow-up period.

Table 12/Column 2:
Persisting from the treatment period into the follow-up period

Same comments as for CCDS apply to US-Labelings and EU-Labelings for Docetaxel Winthropand Taxotere.

GEICAM:
Same comments as for Tax316 comments on slides 9 apply.

☐ Return to LWG *action item(s) if available*
☐ Recommends no changes to labeling
☐ Other *specify*

Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: Font color: Black, Highlight
Formatted: No underline, Font color: Black, Highlight
Formatted: Indent: Left: 0"

EXECUTIVE SUMMARY

SANOFI

Private & Confidential - Page 6 of 7 -

Country Specific Instructions for Submission and Implementation

I. All Direct Action Countries:

(note to RLOM: Only keep applicable timelines. Delete the rest)

Timeline for Submission	Timeline for Industrial Implementation*
Within 90 days from Dispatch of Corporate Package	Within 180 days from Regulatory Authority approval

* Industrial Implementation i.e. release from the manufacturing site

Note: Local regulations may be stricter, in that case Direct Action country to follow their local regulations/guidelines.

II. Reference Countries: Based on information available in SHARE at the date of this letter, the following countries are identified as reference for Docetaxel, and should send a copy of the agency approval letters to the "RnD-GRA-reference-MA" dedicated mailbox upon Regulatory Authority approval: Europe and South Africa.

III. All Deferred Action Countries (countries that need to wait for approval in a reference country):

- Safety Information Letter to be sent to your Regulatory Authority within 21 calendar days after notification by your Global Regulatory Affairs Country/Region Manager (once the safety change in the reference country is submitted).
  - o List of countries exempt from SIL submission is maintained at Region level.

- **Submission and implementation according to the following timelines in the table below:**

Timeline for Submission	Timeline for Industrial Implementation*
After the approval in the reference country and within the timelines required by the submission category rule** to which your country belongs.	Within180 days from Regulatory Authority approval

* Industrial Implementation i.e. QP release from the manufacturing site

** Countries are classified into 3 different categories for submission, i.e.:

{ FILENAME }

EXECUTIVE SUMMARY

SANOFI

Private & Confidential

- "SW90" country: Submission must be done within 90 calendar days after Regional dispatch
- "SW180" country: Submission must be done within 180 calendar days after Regional dispatch
- "SW360" country: Submission must be done within 360 calendar days after Regional dispatch

The country classification used for monitoring is maintained at Region level.

EXHIBIT C

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

****

IN RE: TAXOTERE
(DOCETAXEL) PRODUCTS
LIABILITY LITIGATION

MDL NO. 2740
SECTION "H"

THIS DOCUMENT RELATES TO:
ALL CASES

****

The videotaped CMO 36 trial preservation deposition of ELLEN FEIGAL, PH.D., VOLUME I, taken in connection with the captioned cause, pursuant to the following stipulations before DIXIE VAUGHAN, Certified Court Reporter, January 26, 2023, beginning at 9:44 a.m.

Q. Okay. What are the popular -- what are the popular combination medicines that are used with Taxotere?

A. Well, the effective combination regimens that are used for this indication include Adriamycin, cyclophosphamide, methotrexate, 5FU, and then there are a variety of clinical trials that add other agents that can be used. I think the ones I looked at include Bevacizumab and Gemcitabine.

Q. With regard to Adriamycin, have you investigated whether or not reliable scientific evidence establishes that Adriamycin causes permanent chemotherapy-induced alopecia?

A. No, I do not have evidence to support that. May I also make a comment? I neglected to add Trastuzumab to the list of drugs that I've looked at.

Q. Thank you. I want to get back with Adriamycin. You say that you don't -- I want to make sure I'm repeating what you said. No, you do not have evidence to support that Adriamycin causes permanent chemotherapy-induced alopecia? Is that what you said?

MR. MOORE: Objection to form.

A. Yes, I do not have evidence to support causation.

BY MR. MICELI:

Q. And Adriamycin is the one that's been around since when?

A. I think we said 1974. I'd have to check the textbook on that, but I believe that's the correct date.

Q. And so from 1974 to 2004, did you find any evidence that Adriamycin can cause permanent chemotherapy-induced alopecia?

MR. MOORE: Object to form.

A. No. As I said, all I saw were anecdotal cases. Nothing -- nothing to support causation.

BY MR. MICELI:

Q. I'm going to ask you the same question about cyclophosphamide. And cyclophosphamide has been around since, I think you said, '59?

A. Correct. But check my facts.

Q. Okay. Did you find any reliable scientific evidence that said from between 1959 to 2004, when Taxotere was approved for early-stage breast -- use of adjuvant care in early-stage breast cancer, that cyclophosphamide can cause permanent chemotherapy-induced alopecia?

EXHIBIT D

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF CALIFORNIA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	)	
	)	MDL No. 2740
This Document Relates To:	)	
	)	Section H
Antoinette Durden, Case No. 2:16-cv-17735; Tanya Francis, Case No. 2:16-cv-17410; Barbara Earnest, Case No. 2:16-cv-17144	)	

VIDEOTAPED DEPOSITION OF ELLEN FEIGAL, M.D.
San Francisco, California
Friday, January 11, 2019
Volume III

Reported by:
CARLA SOARES
CSR No. 5908
Job No. 3189948
Pages 384 - 626

SEER registry.

Q Would you agree with me that there have been cases of permanent hair loss reported with Taxol?

A Yes, and I think I have reported it in my table.

Q Would you agree with me that there are cases of permanent hair loss reported with cyclophosphamide?

A I include that in my non-taxane anthracycline cyclophosphamide regimen, yeah.

You're talking about breast cancer; is that correct?

Q Yes.

A Or anything?

Q Breast cancer.

A In breast cancer, yes, and I think I've -- yes.

Q Okay.

A I would agree.

Q Would you agree with me that there are cases of permanent hair loss reported with Adriamycin?

A Yeah. Now, what you're saying is cases reported, yes. I mean, anecdotal reports, yes, I

agree.

Q And there are cases reported of permanent hair loss associated with the AC regimen?

A There have been cases -- anecdotal cases reported.

Q And there have been cases reported of permanent hair loss with the AC Taxol regimen, correct?

A I have captured that in my table. Yes.

Q So yes?

A Yes.

Q And there have been cases of permanent hair loss reported with CMF, correct?

A That I don't think I have a tabulation for.

Q You have not seen that?

A I don't recall seeing that.

By the way, we didn't talk about it, but I have major issues with the Berglund article, which is about CMF.

Q If Dr. Bosserman testified that there have been cases of permanent hair loss reported with CMF, would you have any reason to disagree with her?

MR. THORNTON: Objection. Form.

THE WITNESS: I don't have any opinion on

THE VIDEO OPERATOR: Back on the record. The time is 5:16.

EXAMINATION

BY MR. THORNTON:

Q Yes, Dr. Feigal. I'm going to ask you questions about these articles that you have been presented by counsel for Sanofi, just so you have a chance to make your comments about them as they may relate to your table.

What's your table referred to in your report? I think Table 2?

A Table 2.

Q I thought so.

First of all, as to Crown, what are your observations about the Crown study as it relates to the applicability of that study to Table 2?

A Well, I actually think it's an interesting abstract and poster, which I agree, I hadn't seen.

But upon reading it, I actually think it's supportive of the docetaxel-based regimen inducing permanent alopecia. The largest amount of data is on the docetaxel-based regimen of 265 patients.

There's also a dose response that's present here where patients who received the higher cumulative dose of 450 milligrams -- I presume

that's per meter squared -- had a higher incidence and also a higher degree of severity of their permanent alopecia as compared to a lower dose of the docetaxel-containing regimen.

I do agree that there are anecdotal patients. I believe it's one patient on one of the regimens, and up to three patients on the other, just very small numbers. But basically I believe there's about 39 patients when I did the math on the 265 patients.

So --

Q 39 -- so why don't you go over the numbers -- the actual numbers of patients who are reported in the Crown study as having permanent chemotherapy-induced alopecia.

A So in the Crown study, there's 265 patients who were on a docetaxel regimen, either with or without an anthracycline. There are 12 patients on an anthracycline non-taxane, and there are 23 patients on an anthracycline and a paclitaxel.

And there's approximately 15 percent overall incidence of permanent alopecia for patients receiving docetaxel, and I believe 15 percent of 265 -- I have to do the math, but I believe it was

EXHIBIT E

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION,	MDL No. 2740
This document relates to: Sheila Crayton, Case No. 2:16-cv-05923, Cynthia Thibodeaux, Case No. 2:16-cv-15859	SECTION: H

VIDEOTAPED DEPOSITION OF ELLEN FEIGAL, M.D.
Los Angeles, California
Thursday, November 21, 2019

Stenographically Reported by:
AMANDA J. KALLAS
CSR No. 13901
Job No. 3775935
PAGES 1 - 331

A I said that -- I -- I said I didn't know of any examples; although, there actually may be one, I just didn't highlight it. But what I was instead going to do is in terms of experiment, that a randomized clinical trial is an experiment.

Q Right; a clinical trial --

A And a --

Q -- is an experiment?

A Well, as long as you can answer a question with it.

Q Okay.

A And the question of interest here is Taxotere and permanent alopecia.

Q Okay. And then analogy, in some circumstances, it would be fair to judge by analogy?

A Other than high-dose chemotherapy in the transplant setting, which is well-known, or radiation directly to the scalp, like in patients who get -- who have brain cancer and get direct, there -- there is no analogy to conventional doses of chemo -- of the types of chemotherapy that are given to patients with early-stage breast cancer in the adjuvant setting that cause permanent chemotherapy induced alopecia.

No one's arguing there may be cases recorded,

it on other chemotherapy drugs, but nothing's changed other than this is a new drug. So I can't -- I can't speculate why it's not reported. There's nothing -- there's nothing stopping people from reporting.

Q But you did mention, I think for a second at some point in that answer, that you're not arguing that there are cases of permanent or persisting alopecia associated with other chemotherapy regimens.

A Anecdotal cases.

Q Right.

A Not -- not the level of -- not having the level of evidence that I have with Taxotere. For example, there are no randomized clinical trials with any of these other chemotherapy agents showing an increased incidence of permanent chemotherapy induced alopecia as compared to any other control arm.

Q How do you know that?

A Because I've looked, it's part of my search.

Q Do you have access to the clinical trial data at Bristol-Myers Squibb?

A The scope of what I'm here is about Taxotere. And the litigation is about Taxotere. So my focus

it down by -- by that.

Q Okay. But the point is -- is that there are reports in the medical and scientific literature of cases of permanent chemotherapy induced alopecia following regimens containing Taxol?

A Yes, anecdotal cases.

Q Right.

A And I have that in my table.

Q And also for cytoxan?

A Well, as I said, I have it as a regimen of CMF.

Q Right.

And there are regimens containing cytoxan that do not contain Docetaxel, for which there are reports of permanent chemotherapy induced alopecia in the medical and scientific literature?

A I think there's only one report of 20 that has it, and I think it's Freites-Martin [sic]. I don't think any of the other ones have it with CMF.

Q I'm not talking about CMF.

A I know you're not.

Q I'm talking about regimen --

A I know you're not.

Q So the answer to my question was "yes"?

A No. The answer is, I'm looking at regimens

EXHIBIT F

08:48:06

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION

Docket No.: 16-MD-2740
Section "H(5)"
September 20, 2019
New Orleans, Louisiana

Relates To: Barbara Earnest, Case No.: 16-CV-17144

* *

DAY 5, MORNING SESSION
TRANSCRIPT OF JURY TRIAL PROCEEDINGS
HEARD BEFORE THE HONORABLE JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE

APPEARANCES:

For the Plaintiffs:
Barrios, Kingsdorf & Casteix, LLP
BY: DAWN BARRIOS, ESQ.
701 Poydras Street
Suite 3650
New Orleans, Louisiana 70139

For the Plaintiffs:
Gainsburgh, Benjamin, David, Meunier & Warshauer, LLC
BY: PALMER LAMBERT, ESQ.
2800 Energy Centre
1100 Poydras Street
New Orleans, Louisiana 70163-2800

09:32:57 Q. Thank you.

09:32:59 If I didn't ask this already, does the literature
09:33:02 that you've reviewed support a dose response relationship with
09:33:06 Taxotere?
09:33:06 A. Yeah, from the literature I reviewed, there is evidence
09:33:09 for a dose response.
09:33:17 MR. MICELI: May I have a moment to speak to my --
09:33:20 THE COURT: Sure.
09:33:21 MR. STRONGMAN: Your Honor, may I just grab my
09:33:35 exhibits?
09:33:36 THE COURT: Sure.
09:33:37 EXAMINATION BY MR. MICELI:
09:34:11 Q. Now, Dr. Feigal, because this jury has been told that
09:34:15 A and C may have caused Ms. Earnest's lack of hair regrowth, I
09:34:21 have to ask you, have you reviewed -- in your review of all of
09:34:26 the scientific evidence and medical literature that's out
09:34:28 there, have you seen evidence that A or C has been related --
09:34:34 causally related to permanent irreversible hair loss, hair that
09:34:38 doesn't grow back when it's supposed to?
09:34:41 A. I haven't seen evidence for causal relationship. You'll
09:34:44 see those anecdotal cases that have been reported in the
09:34:48 published literature.
09:34:48 Q. I just want to do a little bit of simple math with you,
09:34:53 based upon your chart. Okay? I guess I can look at it right
09:34:59 here.

EXHIBIT G

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

****

IN RE: TAXOTERE
(DOCETAXEL) PRODUCTS
LIABILITY LITIGATION

MDL NO. 2740
SECTION "H"

THIS DOCUMENT RELATES TO:
ALL CASES

****

The videotaped CMO 36 trial preservation deposition of ELLEN FEIGAL, PH.D., VOLUME II, taken in connection with the captioned cause, pursuant to the following stipulations before DIXIE VAUGHAN, Certified Court Reporter, January 27, 2023, beginning at 8:10 a.m.

A. Correct.

Q. And it's a lengthy expert report, yes?

A. It's an expert report.

Q. Okay. And you included all of your opinions and conclusions. There's a section on conclusions at the end; correct?

A. Yes.

Q. And nowhere in your expert report do you render those opinions, do you? Nowhere in your expert report do you say, "I conducted the analysis and I have determined that Adriamycin cannot cause pCIA"?

A. I do not have that exact sentence, that's correct.

Q. And I think you were asked the same sort of questions about cyclophosphamide and Taxol as well by Mr. Miceli; correct?

A. Correct.

Q. And you didn't have any opinions about whether or not those agents can cause or are capable of causing pCIA in your expert report, did you?

A. In the expert report, I don't have that exact sentence, that's correct.

Q. In fact, you've been deposed numerous

times on your expert report in this case, and every time you were asked that question, whether or not you've made that conclusion, you said, "I didn't do the analysis."

MR. MICELI: Object to the form.

A. Because there wasn't sufficient data to do that analysis. You can't do an analysis on nothing.

BY MR. MOORE:

Q. And if you don't do the analysis, you can't make the conclusion; correct?

MR. MICELI: Objection to form.

A. If there's no data to support it, you can't make the conclusion that it exists.

BY MR. MOORE:

Q. So despite the fact that there are cases of permanent alopecia associated with all of those agents and despite the fact that you did not do an analysis, a causation analysis on those agents, you're still offering the opinion for the first time in this setting that those agents do not cause pCIA; is that what you're trying to tell this jury?

MR. MICELI: Objection to form.

A. I'm not sure it's inconsistent with my

prior depositions where I consistently say there are anecdotal cases, there's not sufficient data to support a causation analysis.

BY MR. MOORE:

Q. Why don't we take a look at what you said in your other deposition, since you brought them up?

A. I'm pretty sure I recall correctly.

Q. You have your binder there? Yes?

A. Yes.

Q. Okay. Let's go to tab 6, if we could, page 83.

A. What page?

Q. Page 83, please.

And I'll read it into the record, starting at line 13.

MR. MICELI: Excuse me. For the record, what we have is excerpts of pages. We may need to have a completeness issued because of where the answers and questions. But go ahead.

BY MR. MOORE:

Q. Beginning on line 13: "In reaching your conclusions about whether Taxotere is capable of causing pCIA, did you determine whether Adriamycin is also capable of causing pCIA?"

"ANSWER: I did not do a Bradford Hill analysis on Adriamycin."

Did I read that correctly?

A. You read it correctly, but it's not complete in the context --

Q. Okay. Well, it's your testimony and the testimony --

A. -- of the rest of the testimony.

Q. Hold on. My question --

MR. MICELI: No, no, no. No, hold on. Excuse me. Objection. You cannot cut her off and tell her: No, no, don't talk anymore.

MR. MOORE: Yeah, I can.

MR. MICELI: No, you can't.

MR. MOORE: N. She has to be responsive to my question.

MR. MICELI: She is being responsive.

MR. MOORE: This is my deposition. It's my time to ask questions. It's no speech --

MR. MICELI: She's telling you it's not complete.

MR. MOORE: No. Now you're testifying. Sit down. You made your form objection. I'm going to continue to examine the witness.

MR. MICELI: We can get the judge if you like. But you cannot instruct her that it's complete when you have page 83 and 97.

MR. MOORE: Okay.

BY MR. MOORE:

Q. Let's read the next question and see if this helps complete it.

"QUESTION": -- on line 19 -- "In reading your conclusion on whether Taxotere is capable of causing pCIA, did you determine whether cyclophosphamide is capable of causing pCIA?"

"ANSWER: I did not do a Bradford Hill analysis on cyclophosphamide."

Did I read that correctly?

A. You're reading an excerpt from a much longer testimony correctly.

Q. I'm reading your sworn testimony correctly; right?

A. You're reading this excerpt of what I said correctly.

Q. Yes, what you said under oath; correct?

MR. MICELI: Object to the form.

A. Everything I said under oath was correct, including the stuff that isn't here.

BY MR. MOORE:

Q. Let me ask you, since you brought up your depositions -- let me ask it, I think, a little differently.

You would agree with me that it is not an appropriate takeaway from your expert report in this case to say that Adriamycin, cyclophosphamide or paclitaxel do not cause pCIA?

A. It's not a yes-or-no answer. Would you like me to explain?

Q. Why don't we look at what you said before. Let's go to tab 7.

MR. MICELI: Objection. Improper impeachment.

BY MR. MOORE:

Q. Okay. So in response to the question I just asked you today under oath, you testified "it's not a yes-or-no answer. Would you like me to explain?" Okay?

Now, you were asked this question, under oath, beginning on line 4:

"QUESTION: Would it be an appropriate takeaway from reading" --

A. I'm sorry. What page are you on?

Q. 141. It's on the screen right there.

MR. MICELI: I'm objecting to the

completeness.

BY MR. MOORE:

Q. "Would it be an appropriate takeaway from reading your report to say that Adriamycin, cyclophosphamide or aromatase inhibitors or paclitaxel do not cause pCIA?"

Miceli objects and then you answer: "What can you say -- what you can say from my report is about the causation of the docetaxel/Taxotere. I'm not opining on other products that aren't the topic for the litigation."

And so then Mr. Insogna continues --

A. Where is this coming from? What deposition is this on?

Q. This is your deposition dated September 1st, 2020.

A. On what?

Q. If you want to look at the caption, the first page is the caption.

A. Right. I'm reading what it's about too. But --

Q. It's about your expert report.

A. Yeah, I know.

Q. And whether or not --

MR. MICELI: Object to the form.

BY MR. MOORE:

Q. And so Mr. Insogna continues: "So I think that answered my question. You could not take away, from reading your report, that those other medicines do not cause pCIA?"

"ANSWER: I'm silent on that." Another objection from Miceli.

And then you go on, "Yeah, I mean, I'm talking about risk and causal association of docetaxel/Taxotere. So, you know, I can't comment any further than that."

Did I read that correctly?

MR. MICELI: Objection.

A. You read --

MR. MICELI: Excuse me, objection on completeness.

A. Yes.

BY MR. MOORE:

Q. Did I read it correctly?

A. You read that excerpt of my testimony correctly.

Q. All right. Let's move over to a new subject matter. You can put the binder down.

A. Okay.

Q. I want to talk about the concept of attribution. I heard you say during your direct examination -- I thought I heard you say that you only -- and to set this up, we're talking about table 2 in your expert report, the one that counts all the cases for the various selected regimens that you put in the column headers. Are you with me?

A. Yeah.

Q. And so I thought I heard you say that you only included a case in the various columns if the author of the study had attributed to that agent? Did I hear that right?

MR. MICELI: Object to the form.

A. To that regimen, I think, is what would be accurate.

BY MR. MOORE:

Q. Okay. So you're not saying that the authors of these studies concluded that it was the Taxotere that caused the event as opposed to the Adriamycin or the cyclophosphamide or the endocrine therapy, if it applies, for whatever study you're talking about? The authors didn't conclude it was Taxotere; correct?

A. The authors -- what I said, the Taxotere

regimen versus the nonTaxotere regimen. So wasn't -- it wasn't seen in the nonTaxotere, seen in the Taxotere regimen.

Q. Okay. What about cases that didn't have other regimens?

A. Well, then I can't do a comparison. But some of them were the -- was Taxotere. So I'm looking at cumulative data.

Q. Right. So --

A. But the regimen is a Taxotere regimen, so that's correct.

Q. So if a study had a case report in it and it was -- it had Taxotere in the regimen, you counted that in the Taxotere column; right?

A. That's correct.

Q. Regardless of whether they took any other chemotherapy agents; correct?

A. That's correct. It wasn't a Taxotere regimen.

Q. And regardless of whether they took endocrine therapy; correct? You still put it in the Taxotere regimen even if they took other chemotherapies and other endocrine therapy; right?

A. The methodologies -- correct, I put a Taxotere regimen in the Taxotere column.

Q. So if it was a Taxotere regimen and a scalp-cooling study, no comparator arm, nothing to compare it to, it goes into the Taxotere column; correct?

A. That's right. That's right.

Q. So when you said that you only included cases where there was attribution, you weren't saying that the authors of those studies attributed the event to Taxotere, you were simply saying those patients had taken Taxotere as part of some regimen and you included it in the Taxotere column?

MR. MICELI: Objection to form.

A. Yeah. I think it was the Taxotere regimen, that's correct. The authors may or might not have attributed it to the Taxotere component, but it was a Taxotere regimen, that's correct.

BY MR. MOORE:

Q. All right. Let's switch gears for a second. I want to ask you about your methodology in collecting the literature. You describe -- I think it is in the footnote, the very first footnote under the table 2. I'll have to get my glasses for this one.

On page 40, footnote 79: "I conducted a

brought it up. Okay.

We'll mark this as Exhibit No. 23.

MR. MOORE: Can we do a two-part exhibit, Dave, and just get the response and the table together, or do you want to make them separate exhibits?

MR. MICELI: I'd rather make them separate exhibits.

MR. MOORE: All right.

MR. MICELI: It will keep it cleaner.

MR. MOORE: Okay. That makes sense.

So Exhibit No. 23, we're going to make the response to agency request, which is dated January of 2013. We'll make that Exhibit 23. And then the accompanying chart, we'll make as Exhibit 24.

(Document marked as EXHIBIT 23 for identification.)

(Document marked as EXHIBIT 24 for identification.)

BY MR. MOORE:

Q. Okay. All right.

In this request, I think this is what you were just talking about. The request says: "It is mentioned in the product information:

Taxotere in combination with doxorubicin and cyclophosphamide: Alopecia grade 3/4 -- alopecia grade 3/4, less than zero, 1 percent."

Do you see that? It says: "Could you please clarify the number/percentage of patients with long-term alopecia following the pivotal breast cancer studies?" Do you see that?

A. Yes.

Q. And this is the response that you're referring to: TAX316 of the TAC group, it says: "728 patients experienced alopecia during the treatment period. Among those patients, alopecia persisted in the post-treatment period in 687 patients. By the end of the follow-up period, 29 patients still had persistent alopecia."

Do you see that?

A. Yes.

Q. Okay. But the person who sent this in to the European agency simply said "by the end of the follow-up period"; correct?

A. That's correct.

Q. He doesn't -- or she doesn't define what the follow-up period is in this submission; right? In the explanation? There's no explanation here as there is in the Canadian document about the

follow-up period for adverse events versus the follow-up period for the entire study?

A. Well, they provided a table, didn't they --

Q. Yes.

A. -- with the same submission, and they said the follow-up duration.

Q. Right. That's what I've marked as --

A. And I have the table.

Q. Right. That's what I have marked as Exhibit 24. Yes?

A. Correct.

Q. Let's take a look at Exhibit 24, if we can.

A. Uh-huh.

Q. Okay. Okay. So what we see here in table 20 -- in Exhibit 24, the table accompanying the European submission, you're correct they state: "Date of last follow-up."

MR. MICELI: I'm going to object to the form to the question, but go ahead.

MR. MOORE: What did I say?

MR. MICELI: You said this is to the European agency.

MR. MOORE: Right.

MR. MICELI: I'll clear it up on redirect.
MR. MOORE: All right.
A. I mean, it says "Kapreski." Is that -- what am I looking at?
BY MR. MICELI:
Q. That's just an exhibit stamp. That's just an exhibit stamp.
Let's just talk about with this table, wherever it was, whether it came from --
A. Okay.
Q. -- whether it was submitted to the European, Dave will tell us what it's about.
But this table, you would agree, includes the same type of columns at the top; right?
A. Well, it is important to know whether -- what was submitted to the European agency. But I can read what's on here. I'm just not -- I'm not clear if this is actually the table that was submitted.
Q. Okay.
A. So I think it would be a bit misleading. I mean, I want to see what was submitted to the agency.
MR. MOORE: Let's go off the record for a

second.

THE VIDEOGRAPHER: We're off the record, 9:16 a.m.

(Recess taken at 9:16 a.m. Back on record at 9:18 a.m.)

THE VIDEOGRAPHER: We're back on the record, 9:18 a.m.

BY MR. MOORE:

Q. All right. Back to Exhibit 24. And Mr. Miceli will probably have some questions for you about this exhibit. I may have referred to it as being attached to the European submission. It may be a slightly later version because I do note there's a date down here on the data run of March of 2012 -- well, it may be earlier, but Mr. Miceli will clear that up if it's material.

A. Okay.

Q. But what I really want to focus on, though, is that wherever this data is going and for whatever purpose, if it's comparable to what was sent to the European regulator or if it's just run for another reason.

A. Okay.

Q. What this shows or what my question was, was about the headers, where it has: "Preferred

term, Treatment arm, Subject ID, Date of last IV plus 30 days, Date of last follow-up, follow-up duration (years)." Do you see that?

A. Yes.

Q. And those are the same headers that are in the response to the Canadian regulator except there's one difference. This column that says: "Date of last follow-up of adverse event" in the Canadian document and then in the other table, it says: "Date of last follow-up."

A. Yeah, I can see that.

Q. Okay. All right. And the dates that they give, it's the exact same patients, the first patient's 11702, first patient in Canadian chart, 11702. Duration 10.04 years. They're the same?

A. Yeah. I see that.

Q. But then the next patient, 11724: Follow-up duration of last follow-up, 6.57 years; Follow-up duration, last follow-up of adverse event, 2.96. Do you see that? Here?

A. I'm sorry. Where are you? What line are you on?

Q. I'm right here. So this patient, Follow-up duration 2.96 years in the Canadian chart --

A. I don't see the two-point -- I'm so sorry. I did not see the 2.96.

Q. Sorry.

A. There it is. It wasn't on the screen. Thank you.

Q. I'm sorry. And that's different than the number that's captured in Exhibit 24; correct?

A. Yes, it is.

Q. All right. And then look at this third patient in Exhibit 24. They were only followed for .32 years. Do you see that?

A. Yes, I do see that.

Q. And .32 years is an insufficient duration of follow-up to determine if that patient has permanent chemotherapy-induced alopecia.

A. If that's correct, that would be less than six months, that's correct.

Q. And so what I want to do is just ask you, given that we have these two tables, both coming from Sanofi, one definitely submitted to a regulator, one -- maybe it was or maybe there's a similar version submitted to a regulator -- that have different follow-up periods. How can we figure out which one's correct?

MR. MICELI: Objection to form.

A. Well, you're talking about apples and oranges. The follow-up that Sanofi did submit to the European agency in response to their question about persistent or long-lasting permanent alopecia came back with 29 and 16. That's Sanofi. I'm not manipulating the numbers. That is what they told the agency.

BY MR. MOORE:

Q. Yes.

A. In response to the question about permanent alopecia, that was their response. And that's actually what's on their label.

MR. MOORE: Move to strike.

BY MR. MOORE:

Q. So the statement you just made, the statement you just made is inconsistent with the highlighted statement at the bottom of the last paragraph submitted to the Canadian regulator; correct?

A. Now which document are you talking about?

Q. I'm going back to Exhibit No. 22.

A. So you're going back to the Canadian document?

Q. Yes.

A. I'm talking about the European document.
Q. My question is about the Canadian document.
A. In the Canadian document, it sounds like they can't be precise, it's ongoing. I'm not assuming. It resolved immediately.
Q. You're assuming --
A. Defini- -- I'm not assuming. I'm just going by the Sanofi definition. It was ongoing.
Q. You're assuming that if it was ongoing at -- let's just take a look at some of the patients. You're assuming that for patient 11738, who was last followed for the adverse event for only .24 years, less than three months, you're assuming that that person's alopecia never resolved, even though they weren't followed for alopecia after that time. That's an assumption built into the conclusion you're drawing; correct?
A. I am going by Sanofi's definition of how they describe ongoing alopecia and how they responded to a federal agency's request for long-term permanent alopecia and what is on their label.
Q. And their response in the Canadian document to a federal regulator was: "Thus,

ongoing does not necessarily mean that these adverse events were ongoing for the entire ten-year follow-up period; rather, it means that they were noted as ongoing at the last follow-up visit." Right?

A.   You're reading that sentence correctly.

Q.   Okay. And that's a sentence that you are ignoring in favor of the statement that you like better to the European regulator; correct?

MR. MICELI: Object to the form.

A.   No. That wouldn't be an appropriate characterization of what I'm trying to communicate.

BY MR. MOORE:

Q.   Okay.

A.   Sanofi is the sponsor of this study. Sanofi set the definitions. Sanofi is sending information to regulatory agencies and Sanofi is responsible for their label, which currently still reads 29 and 16.

MR. MOORE: Move to strike.

BY MR. MOORE:

Q.   Doctor, you would agree that the information communicated in these two submissions, can we at least agree it's inconsistent?

A. I'm sorry, I couldn't hear your last word.

Q. Can we at least agree that the statements made in the two submissions that we showed you, the Canadian submission and the other submission, would you agree that they're inconsistent?

A. Not necessarily.

Q. If you wanted to know -- just based on the information that I showed you, if you said: You know what, maybe I need to see if they really were followed for more than six months, the way to do that would be to look at the case report forms for the 29 patients to see what happened to them; right?

A. No.

Q. When you were doing clinical trials, you're aware that the clinical information for the patients are captured in case report forms for every single patient in the study. That's something that happens?

A. Yes. And Sanofi is aware of it and did that.

Q. Right. And those case report forms, the clinical data for all 29 of these patients is

analysis of the entire trial.

BY MR. MOORE:

Q. If those patients were not followed for alopecia for more than six months, then they do not have permanent chemotherapy-induced alopecia; correct?

MR. MICELI: Object to the form.

A. They were followed for more than six months except for that one that may have had .32 follow-up. All of them were followed for longer.

BY MR. MOORE:

Q. Were they followed for the adverse event for longer than six months?

A. Sanofi is in charge of their database, not me. And they're the ones who responded to a very specific question about how many long-term, permanent alopecia cases you have on the TAC and the FAC. And Sanofi answered them. I'm not doing a post hoc look at a subset of documents. That's not the appropriate way to evaluate this.

Q. Okay. But we're not in a scientific classroom. We're not in --

A. Clearly.

Q. -- a scientific setting. You're not

giving a lecture on statistics to a bunch of students. You're in front of a jury in a courtroom and in a courtroom, the truth matters, and the truth about whether those patients were followed for more than six months for alopecia is in the case report forms, isn't it?

MR. MICELI: Object to the form.

A. No.

BY MR. MOORE:

Q. Let's look at one, then. Let's just look at one.

MR. MICELI: We'll mark this as Exhibit Number 25.

(Document marked as EXHIBIT 25 for identification.)

BY MR. MOORE:

Q. Okay. What I've handed you, Doctor, as Exhibit No. 25 are pages from the confidential patient data for Patient No. 15002. Do you see that?

A. Yes.

Q. Okay. And this is the type of document that records the clinical data for a clinical study participant; correct?

A. I've just been handed it. I assume

EXHIBIT H

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA
CASE NO. 2:16-cv-17039

ELIZABETH KAHN, Plaintiff, v. SANOFI S.A., SANOFI-AVENTIS U.S. L.L.C., SANOFI US SERVICE, INC., and AVENTIS-PHARMA S.A., Defendants.	) VIDEOCONFERENCE VIDEOTAPED) DEPOSITION OF:)) ELLEN G. FEIGAL, M.D.

CONFIDENTIAL

TRANSCRIPT of the stenographic notes of the proceedings in the above-entitled matter, as taken by and before ELLEN J. GODINO, CCR, RPR, CRCR, held via Zoom videoconference from multiple locations, with the witness located at 11806 Barranca Road, Santa Rosa Valley, California, on Friday, April 10, 2020, commencing at 10:58 a.m.

is capable of causing PCIA, you did not analyze whether Adriamycin, cyclophosphamide, Xeloda, Gemzar or Avastin are also capable of causing PCIA. Correct?

MR. MICELI: Object to the form.

A. I analyzed those drugs in the context of answering the question about Taxotere. I found no evidence, to the degree I found it with Taxotere, for general causation. But no, I did not do general causation analysis on any of the chemotherapy drugs, other than Taxotere.

Q. So let me try and understand --

A. What I just said is a correct statement.

Q. Okay. So you did not perform a general causation analysis on any other chemotherapy drugs besides Taxotere. Right?

A. Yes. But I did look at the drugs in the regimen, and did my analysis based on the literature, the randomized controlled clinical trials, and the pharmacovigilance.

Q. And so let's say hypothetically that you reviewed a paper that had 50 cases of PCIA in non-Taxotere regimens. That would not be sufficient for you to conclude that those drugs are capable of causing PCIA. Right?

EXHIBIT I

FILE PRODUCED NATIVELY

SANOFI

RESPONSE TO AGENCY REQUEST

INFORMATION ON ALOPECIA TOPIC DATED ON 26-Nov-2012

Date: 22 January 2013 Total number of pages: 2

TABLE OF CONTENTS

TITLE PAGE 1

TABLE OF CONTENTS 2

AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 1: 3

AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 1:

It is mentioned in the product information: "Taxotere in combination with doxorubicin and cyclophosphamide: alopecia G3/4: <0,1%". Could you please clarify the number/percentage of patients with long term/permanent alopecia from the pivotal breast cancer studies?

Sanofi response:

The MAH provides below the following data that illustrate the frequency and incidence of patients with persistent alopecia, respectively from the pivotal breast cancer studies TAX316 and GEICAM9805:

- TAX316: in the TAC group, 728 (97.8%) patients experienced alopecia during the treatment period. Among those patients, alopecia persisted into the post-treatment period in 687 patients (92.3%). By the end of the follow-up period, 29 TAC patients (4.2%) still had persistent alopecia. In the FAC group, a total of 715 patients (97.1%) experienced alopecia during treatment, including 645 patients (87.6%) with alopecia persisting during the follow-up period. By the end of the follow-up period, 16 FAC patients (2.5%) still had persistent alopecia.

- GEICAM9805: in the TAC group, 514 (96.6%) patients experienced alopecia during the treatment period. Among those patients, alopecia persisted into the post-treatment period in 49 patients (9.2%). By the end of the follow-up period, 3 TAC patients (6.1%) still had persistent alopecia. In the FAC group, a total of 508 patients (97.9%) had alopecia during treatment, including 35 patients (6.7%) with alopecia persisting during the follow-up period. By the end of the follow-up period, 1 FAC patient (2.9%) still had persistent alopecia.

Section 4.8 of the SmPC of docetaxel mentions that alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 TAC patients and 645 FAC patients in study TAX316. At the end of the follow-up period, alopecia was observed to be ongoing in 29 TAC patients (4.2%) and 16 FAC patients (2.4%). In its postmarketing section, the SmPC mentions also that cases of persisting alopecia have been reported.

EXHIBIT J

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAXOTERE safely and effectively. See full prescribing information for TAXOTERE.

TAXOTERE (docetaxel) injection, for intravenous use
Initial U.S. Approval: 1996

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

See full prescribing information for complete boxed warning.

- **Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving TAXOTERE at 100 mg/m^2 (5.1)**
- **Avoid use of TAXOTERE if bilirubin > ULN, or if AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN. LFT elevations increase risk of severe or life-threatening complications. Obtain LFTs before each treatment cycle (5.2)**
- **Do not administer TAXOTERE to patients with neutrophil counts <1500 cells/mm^3. Obtain frequent blood counts to monitor for neutropenia (4, 5.3)**
- **Severe hypersensitivity, including fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of TAXOTERE and administration of appropriate therapy (5.5)**
- **Contraindicated if history of severe hypersensitivity reactions to TAXOTERE or to drugs formulated with polysorbate 80 (4)**
- **Severe fluid retention may occur despite dexamethasone (5.6)**

----------INDICATIONS AND USAGE----------
TAXOTERE is a microtubule inhibitor indicated for:

- **Breast Cancer (BC)**: single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC (1.1)
- **Non-small Cell Lung Cancer (NSCLC)**: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC (1.2)
- **Castration-Resistant Prostate Cancer (CRPC)**: with prednisone in metastatic castration-resistant prostate cancer (1.3)
- **Gastric Adenocarcinoma (GC)**: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (1.4)
- **Squamous Cell Carcinoma of the Head and Neck (SCCHN)**: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

----------DOSAGE AND ADMINISTRATION----------
Administer in a facility equipped to manage possible complications (e.g., anaphylaxis). Administer intravenously (IV) over 1 hr every 3 weeks. PVC equipment is not recommended. **Use only a 21 gauge needle to withdraw TAXOTERE from the vial.**

- BC locally advanced or metastatic: 60 mg/m^2 to 100 mg/m^2 single agent (2.1)
- BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (2.1)
- NSCLC: after platinum therapy failure: 75 mg/m^2 single agent (2.2)
- NSCLC: chemotherapy naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (2.2)
- HRPC: 75 mg/m^2 with 5 mg prednisone twice a day continuously (2.3)
- GC: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion (2.4)
- SCCHN: 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles (2.5)
- SCCHN: 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1-4); for 3 cycles (2.5)

For all patients:

- Premedicate with oral corticosteroids (2.6)
- Adjust dose as needed (2.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: One-vial TAXOTERE: Single-dose vials 20 mg/mL and 80 mg/4 mL (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to docetaxel or polysorbate 80 (4)
- Neutrophil counts of <1500 cells/mm^3 (4)

----------WARNINGS AND PRECAUTIONS----------

- Second primary malignancies: In patients treated with TAXOTERE-containing regimens, monitor for delayed AML, MDS, NHL, and renal cancer. (5.7)
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe cutaneous adverse reactions have been reported. Severe skin toxicity may require dose adjustment or permanent treatment discontinuation. (5.8)
- Neurologic reactions: Reactions including paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent. (5.9)
- Eye disorders: Cystoid macular edema (CME) has been reported and requires treatment discontinuation. (5.10)
- Asthenia: Severe asthenia may occur and may require treatment discontinuation. (5.11)
- Embryo-fetal toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.12, 8.1, 8.3)
- Alcohol content: The alcohol content in a dose of TAXOTERE Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion. (5.13)
- Tumor lysis syndrome: Tumor lysis syndrome has been reported. Patients at risk should be well hydrated and closely monitored during treatment. (5.14)

----------ADVERSE REACTIONS----------
Most common adverse reactions across all TAXOTERE indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of TAXOTERE. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION
1 INDICATIONS AND USAGE
1.1 Breast Cancer
1.2 Non-small Cell Lung Cancer
1.3 Prostate Cancer
1.4 Gastric Adenocarcinoma
1.5 Head and Neck Cancer
2 DOSAGE AND ADMINISTRATION
2.1 Breast Cancer
2.2 Non-small Cell Lung Cancer
2.3 Prostate Cancer
2.4 Gastric Adenocarcinoma
2.5 Head and Neck Cancer
2.6 Premedication Regimen
2.7 Dosage Adjustments during Treatment

2.8 Administration Precautions
2.9 Preparation and Administration
2.10 Stability
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Toxic Deaths
5.2 Hepatic Impairment
5.3 Hematologic Effects
5.4 Enterocolitis and Neutropenic Colitis
5.5 Hypersensitivity Reactions
5.6 Fluid Retention
5.7 Second Primary Malignancies
5.8 Cutaneous Reactions
5.9 Neurologic Reactions
5.10 Eye Disorders
5.11 Asthenia
5.12 Embryo-Fetal Toxicity
5.13 Alcohol Content
5.14 Tumor Lysis Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Locally Advanced or Metastatic Breast Cancer
14.2 Adjuvant Treatment of Breast Cancer
14.3 Non-small Cell Lung Cancer (NSCLC)
14.4 Castration-Resistant Prostate Cancer
14.5 Gastric Adenocarcinoma
14.6 Head and Neck Cancer
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage
16.3 Handling and Disposal
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

Treatment-related mortality associated with TAXOTERE is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive TAXOTERE as a single agent at a dose of 100 mg/m^2 *[see Warnings and Precautions (5.1)]*.

Avoid the use of TAXOTERE in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 × ULN also had a higher rate of febrile neutropenia. Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of TAXOTERE *[see Warnings and Precautions (5.2)]*.

Do not administer TAXOTERE to patients with neutrophil counts of <1500 cells/mm^3. Monitor blood counts frequently as neutropenia may be severe and result in infection. *[see Warnings and Precautions (5.3)]*.

Do not administer TAXOTERE to patients who have a history of severe hypersensitivity reactions to TAXOTERE or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*. Severe hypersensitivity reactions have been reported in patients despite dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and administration of appropriate therapy *[see Warnings and Precautions (5.5)]*.

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of dexamethasone premedication. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) *[see Warnings and Precautions (5.6)]*.

1 INDICATIONS AND USAGE

1.1 Breast Cancer

TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

TAXOTERE in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

1.2 Non-small Cell Lung Cancer

TAXOTERE as a single agent is indicated for the treatment of patients with locally advanced or

metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

TAXOTERE in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

1.3 Prostate Cancer

TAXOTERE in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

1.4 Gastric Adenocarcinoma

TAXOTERE in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

1.5 Head and Neck Cancer

TAXOTERE in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

2 DOSAGE AND ADMINISTRATION

For all indications, toxicities may warrant dosage adjustments *[see Dosage and Administration (2.7)]*.

Administer in a facility equipped to manage possible complications (e.g. anaphylaxis).

2.1 Breast Cancer

- For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of TAXOTERE is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
- For the adjuvant treatment of operable node-positive breast cancer, the recommended TAXOTERE dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities *[see Dosage and Administration (2.7)]*.

2.2 Non-small Cell Lung Cancer

- For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized controlled trials *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5), Clinical Studies (14)]*.
- For chemotherapy-naive patients, TAXOTERE was evaluated in combination with cisplatin. The recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks *[see Dosage and Administration (2.7)]*.

2.3 Prostate Cancer

- For metastatic castration-resistant prostate cancer, the recommended dose of TAXOTERE is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously *[see Dosage and Administration (2.7)]*.

2.4 Gastric Adenocarcinoma

- For gastric adenocarcinoma, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration *[see Dosage and Administration (2.7)]*.

2.5 Head and Neck Cancer

Patients must receive premedication with antiemetics, and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. All patients treated on the TAXOTERE containing arms of the TAX323 and TAX324 studies received prophylactic antibiotics.

Induction Chemotherapy Followed by Radiotherapy (TAX323)

For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy *[see Dosage and Administration (2.7)]*.

Induction Chemotherapy Followed by Chemoradiotherapy (TAX324)

For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy *[see Dosage and Administration (2.7)]*.

2.6 Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to TAXOTERE administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.5)]*.

For metastatic castration-resistant prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before the TAXOTERE infusion *[see Warnings and Precautions (5.5)]*.

2.7 Dosage Adjustments during Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during TAXOTERE therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE therapy may tolerate higher doses. Patients who develop ≥grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast Cancer

TAXOTERE in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their TAXOTERE dose reduced to 60 mg/m^2. Patients who experience grade 3 or 4 stomatitis should have their TAXOTERE dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXOTERE therapy should have their dosage of TAXOTERE reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Non-small Cell Lung Cancer

Monotherapy with TAXOTERE for NSCLC treatment after failure of prior platinum-based chemotherapy

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination therapy with TAXOTERE for chemotherapy-naive NSCLC

For patients who are dosed initially at TAXOTERE 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer

Combination therapy with TAXOTERE for metastatic castration-resistant prostate cancer

TAXOTERE should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe

or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXOTERE therapy should have the dosage of TAXOTERE reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Gastric or Head and Neck Cancer

TAXOTERE in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer

Patients treated with TAXOTERE in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the TAXOTERE dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the TAXOTERE dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia the TAXOTERE dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Do not retreat patients with subsequent cycles of TAXOTERE until neutrophils recover to a level >1,500 cells/mm^3 *[see Contraindications (4)]*. Avoid retreating patients until platelets recover to a level >100,000 cells/mm^3. Discontinue treatment if these toxicities persist *[see Warnings and Precautions (5.3)]*.

Recommended dose modifications for toxicities in patients treated with TAXOTERE in combination with cisplatin and fluorouracil are shown in Table 1.

Table 1: Recommended Dose Modifications for Toxicities in Patients Treated with TAXOTERE in Combination with Cisplatin and Fluorouracil

Toxicity	Dosage adjustment
Diarrhea grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: then reduce TAXOTERE dose by 20%.
Diarrhea grade 4	First episode: reduce TAXOTERE and fluorouracil doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: stop fluorouracil only, at all subsequent cycles. Third episode: reduce TAXOTERE dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop fluorouracil only, at all subsequent cycles. Second episode: reduce TAXOTERE dose by 20%.

Liver dysfunction: In case of AST/ALT >2.5 to ≤5 × ULN and AP ≤2.5 × ULN, or AST/ALT >1.5 to ≤5 × ULN and AP >2.5 to ≤5 × ULN, TAXOTERE should be reduced by 20%.

In case of AST/ALT >5 × ULN and/or AP >5 × ULN TAXOTERE should be stopped.

The dose modifications for cisplatin and fluorouracil in the gastric cancer study are provided below.

Cisplatin dose modifications and delays

Peripheral neuropathy: A neurological examination should be performed before entry into the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs

or symptoms, more frequent examinations should be performed and the following dose modifications can be made according to NCI-CTCAE grade:

- Grade 2: Reduce cisplatin dose by 20%.
- Grade 3: Discontinue treatment.

Ototoxicity: In the case of grade 3 toxicity, discontinue treatment.

Nephrotoxicity: In the event of a rise in serum creatinine ≥grade 2 (>1.5 × normal value) despite adequate rehydration, CrCl should be determined before each subsequent cycle and the following dose reductions should be considered (see Table 2).

For other cisplatin dosage adjustments, also refer to the manufacturers' prescribing information.

Table 2: Dose Reductions for Evaluation of Creatinine Clearance

Creatinine clearance result before next cycle	**Cisplatin dose next cycle**
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was reinstituted at the next cycle. If no recovery was observed, then cisplatin was omitted from the next treatment cycle.
CrCl <40 mL/min	Dose of cisplatin was omitted in that treatment cycle only. If CrCl was still <40 mL/min at the end of cycle, cisplatin was discontinued. If CrCl was >40 and <60 mL/min at end of cycle, a 50% cisplatin dose was given at the next cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was given at next cycle.

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays

For diarrhea and stomatitis, see Table 1.

In the event of grade 2 or greater plantar-palmar toxicity, fluorouracil should be stopped until recovery. The fluorouracil dosage should be reduced by 20%.

For other greater than grade 3 toxicities, except alopecia and anemia, chemotherapy should be delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade ≤1 and then recommenced, if medically appropriate.

For other fluorouracil dosage adjustments, also refer to the manufacturers' prescribing information.

Combination Therapy with Strong CYP3A4 Inhibitors

Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require coadministration of a strong CYP3A4 inhibitor *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

2.8 Administration Precautions

TAXOTERE is a hazardous anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended *[see How Supplied/Storage and Handling (16.3)]*.

If TAXOTERE Injection initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE Injection initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

One-vial TAXOTERE (Injection)

TAXOTERE Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Please follow the preparation instructions provided below.

2.9 Preparation and Administration

DO NOT use the two-vial formulation (Injection and diluent) with the one-vial formulation.

One-vial TAXOTERE (Injection)

TAXOTERE Injection (20 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw TAXOTERE from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. TAXOTERE vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection vials to stand at room temperature for approximately 5 minutes before use.
2. Using **only** a 21 gauge needle, aseptically withdraw the required amount of TAXOTERE injection (20 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.

If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.

3. Thoroughly mix the infusion by gentle manual rotation.
4. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.
5. TAXOTERE infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

The TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

2.10 Stability

TAXOTERE final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. TAXOTERE final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36°F and 46°F).

3 DOSAGE FORMS AND STRENGTHS

One-vial TAXOTERE (Injection)

TAXOTERE 20 mg/mL

TAXOTERE (docetaxel) Injection 20 mg/1 mL single-dose vial: 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

TAXOTERE 80 mg/4 mL

TAXOTERE (docetaxel) Injection 80 mg/4 mL single-dose vial: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

4 CONTRAINDICATIONS

TAXOTERE is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm^3 *[see Warnings and Precautions (5.3)]*.
- a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Toxic Deaths

Breast Cancer

TAXOTERE administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-small Cell Lung Cancer

TAXOTERE administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry *[see Dosage and Administration (2.2), Clinical Studies (14)]*.

5.2 Hepatic Impairment

Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death.

Avoid TAXOTERE in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN *[see Warnings and Precautions (5.1)]*.

For patients with isolated elevations of transaminase >1.5 × ULN, consider TAXOTERE dose modifications *[see Dosage and Administration (2.7)]*.

Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of TAXOTERE therapy.

5.3 Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving TAXOTERE. Do not retreat patients with subsequent cycles of TAXOTERE until neutrophils recover to a level >1500 cells/mm^3 *[see Contraindications (4)]*. Avoid retreating patients until platelets recover to a level >100,000 cells/mm^3.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle *[see Dosage and Administration (2.7)]*.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of TAXOTERE and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients

given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to patients with neutrophils <1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection *[see Dosage and Administration (2.7), Adverse Reactions (6)]*.

5.4 Enterocolitis and Neutropenic Colitis

Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with TAXOTERE alone and in combination with other chemotherapeutic agents, despite the coadministration of G-CSF. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new, or worsening symptoms of gastrointestinal toxicity *[see Dosage and Administration (2), Warnings and Precautions (5.3), Adverse Reactions (6.2)]*.

5.5 Hypersensitivity Reactions

Monitor patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and aggressive therapy. Do not rechallenge patients with a history of severe hypersensitivity reactions with TAXOTERE *[see Contraindications (4)]*.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a hypersensitivity reaction to docetaxel that may include severe or fatal reactions such as anaphylaxis. Monitor patients with a previous history of hypersensitivity to paclitaxel closely during initiation of TAXOTERE therapy. Hypersensitivity reactions may occur within a few minutes following initiation of a TAXOTERE infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of TAXOTERE *[see Dosage and Administration (2.6)]*.

5.6 Fluid Retention

Severe fluid retention has been reported following TAXOTERE therapy. Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to reduce the incidence and severity of fluid retention *[see Dosage and Administration (2.6)]*. Patients with pre-existing effusions should be closely monitored from the first dose for the possible

exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. Nine of 92 patients (9.8%) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of TAXOTERE to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s).

5.7 Second Primary Malignancies

Second primary malignancies, notably acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), and renal cancer, have been reported in patients treated with docetaxel-containing regimens. These adverse reactions may occur several months or years after docetaxel-containing therapy.

Treatment-related AML or MDS has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (TAX316) AML occurred in 3 of 744 patients who received TAXOTERE, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin, and cyclophosphamide *[see Clinical Studies (14.2)]*. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up. Monitor patients for second primary malignancies *[see Adverse Reactions (6.1)]*.

5.8 Cutaneous Reactions

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended *[see Dosage and Administration (2.7)]*. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued TAXOTERE due to skin toxicity.

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Permanent treatment discontinuation should be considered in patients who experience SCARs.

5.9 Neurologic Reactions

Severe neurosensory symptoms (e.g. paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued *[see Dosage and Administration (2.7)]*. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was

available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

5.10 Eye Disorders

Cystoid macular edema (CME) has been reported in patients treated with TAXOTERE. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, TAXOTERE treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered.

5.11 Asthenia

Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

5.12 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and its mechanism of action, TAXOTERE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating TAXOTERE. Advise females of reproductive potential to use effective contraception during treatment and for 2 months after the last dose of TAXOTERE. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of TAXOTERE *[see Use in Specific Populations (8.1, 8.3)]*.

5.13 Alcohol Content

Cases of intoxication have been reported with some formulations of docetaxel due to the alcohol content. The alcohol content in a dose of TAXOTERE Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in TAXOTERE Injection on the ability to drive or use machines immediately after the infusion. Each administration of TAXOTERE Injection at 100 mg/m^2 delivers 2.0 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 4.0 grams of ethanol *[see Description (11)]*. Other docetaxel products may have a different amount of alcohol.

5.14 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with docetaxel *[see Adverse Reactions (6.2)]*. Patients at risk of tumor lysis syndrome (e.g., with renal impairment, hyperuricemia, bulky tumor) should be closely monitored prior to initiating TAXOTERE and periodically during treatment. Correction of dehydration and treatment of high uric acid levels are recommended prior to

initiation of treatment.

6 ADVERSE REACTIONS

The most serious adverse reactions from TAXOTERE are:

- Toxic Deaths *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hepatic Impairment *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Hematologic Effects *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Enterocolitis and Neutropenic Colitis *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Boxed Warning, Warnings and Precautions (5.5)]*
- Fluid Retention *[see Boxed Warning, Warnings and Precautions (5.6)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.7)]*
- Cutaneous Reactions *[see Warnings and Precautions (5.8)]*
- Neurologic Reactions *[see Warnings and Precautions (5.9)]*
- Eye Disorders *[see Warnings and Precautions (5.10)]*
- Asthenia *[see Warnings and Precautions (5.11)]*
- Alcohol Content *[see Warnings and Precautions (5.13)]*

The most common adverse reactions across all TAXOTERE indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

6.1 Clinical Trials Experience

Breast Cancer

Monotherapy with TAXOTERE for locally advanced or metastatic breast cancer after failure of prior chemotherapy

TAXOTERE 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both

previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to TAXOTERE. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving TAXOTERE for the treatment of breast cancer and in patients with other tumor types. (See Table 3.)

Table 3: Summary of Adverse Reactions in Patients Receiving TAXOTERE at 100 mg/m^2

Adverse Reaction	**All Tumor Types Normal LFTs* n=2045 %**	**All Tumor Types Elevated LFTs** n=61 %**	**Breast Cancer Normal LFTs* n=965 %**
Hematologic			
Neutropenia			
<2000 cells/mm^3	96	96	99
<500 cells/mm^3	75	88	86
Leukopenia			
<4000 cells/mm^3	96	98	99
<1000 cells/mm^3	32	47	44
Thrombocytopenia			
<100,000 cells/mm^3	8	25	9
Anemia			
<11 g/dL	90	92	94
<8 g/dL	9	31	8
Febrile Neutropenia***	11	26	12
Septic Death	2	5	1
Non-Septic Death	1	7	1
Infections			
Any	22	33	22
Severe	6	16	6
Fever in Absence of Infection			
Any	31	41	35
Severe	2	8	2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21	20	18
Severe	4	10	3
With 3-day Premedication	n=92	n=3	n=92
Any	15	33	15
Severe	2	0	2
Fluid Retention			
Regardless of Premedication			

Adverse Reaction	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Any	47	39	60
Severe	7	8	9
With 3-day Premedication	n=92	n=3	n=92
Any	64	67	64
Severe	7	33	7
Neurosensory			
Any	49	34	58
Severe	4	0	6
Cutaneous			
Any	48	54	47
Severe	5	10	5
Nail Changes			
Any	31	23	41
Severe	3	5	4
Gastrointestinal			
Nausea	39	38	42
Vomiting	22	23	23
Diarrhea	39	33	43
Severe	5	5	6
Stomatitis			
Any	42	49	52
Severe	6	13	7
Alopecia	76	62	74
Asthenia			
Any	62	53	66
Severe	13	25	15
Myalgia			
Any	19	16	21
Severe	2	2	2
Arthralgia	9	7	8
Infusion Site Reactions	4	3	4

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline LFTs: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization

Hematologic reactions

Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE *[see Warnings and Precautions (5.3)]*. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid

tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm^3 with fever >38°C with intravenous antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity reactions

Severe hypersensitivity reactions have been reported *[see Boxed Warning, Warnings and* Precautions *(5.5)]*. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and instituting appropriate therapy.

Fluid retention

Fluid retention can occur with the use of TAXOTERE *[see Boxed Warning, Dosage and Administration (2.6), Warnings and Precautions (5.6)]*.

Cutaneous reactions

Severe skin toxicity is discussed elsewhere in the label *[see Warnings and Precautions (5.8)]*. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after TAXOTERE infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Neurologic reactions

Neurologic reactions are discussed elsewhere in the label *[see Warnings and Precautions (5.9)]*.

Gastrointestinal reactions

Nausea, vomiting, and diarrhea were generally mild to moderate. Severe reactions occurred in 3%-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular reactions

Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically

meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension have occurred. Seven of 86 (8.1%) of metastatic breast cancer patients receiving TAXOTERE 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥10% associated with a drop below the institutional lower limit of normal.

Infusion site reactions

Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

Hepatic reactions

In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in AST or ALT >1.5 times the ULN, or alkaline phosphatase >2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on TAXOTERE, increases in AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. Whether these changes were related to the drug or underlying disease has not been established.

Hematologic and other toxicity: Relation to dose and baseline liver chemistry abnormalities

Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given TAXOTERE at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN); and 174 patients in Japanese studies given TAXOTERE at 60 mg/m^2 who had normal LFTs (see Tables 4 and 5).

Table 4: Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Adverse Reaction	TAXOTERE 100 mg/m^2		TAXOTERE 60 mg/m^2
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Neutropenia			
Any <2000 cells/mm^3	98	100	95
Grade 4 <500 cells/mm^3	84	94	75
Thrombocytopenia			
Any <100,000 cells/mm^3	11	44	14
Grade 4 <20,000 cells/mm^3	1	17	1
Anemia <11 g/dL	95	94	65
Infection* **			
Any	23	39	1

Adverse Reaction	TAXOTERE 100 mg/m²		TAXOTERE 60 mg/m²
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Grade 3 and 4	7	33	0
Febrile Neutropenia**			
By Patient	12	33	0
By Course	2	9	0
Septic Death	2	6	1
Non-Septic Death	1	11	0

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline LFTs: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Incidence of infection requiring hospitalization and/or intravenous antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.

****Febrile Neutropenia: For 100 mg/m², ANC grade 4 and fever >38°C with intravenous antibiotics and/or hospitalization; for 60 mg/m², ANC grade 3/4 and fever >38.1°C

Table 5: Non-hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m² with Normal or Elevated Liver Function Tests or 60 mg/m² with Normal Liver Function Tests

Adverse Reaction	TAXOTERE 100 mg/m²		TAXOTERE 60 mg/m²
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13	6	1
Severe	1	0	0
Fluid Retention* Regardless of Premedication**			
Any	56	61	13
Severe	8	17	0
Neurosensory			
Any	57	50	20
Severe	6	0	0
Myalgia	23	33	3
Cutaneous			
Any	45	61	31

Adverse Reaction	TAXOTERE 100 mg/m^2		TAXOTERE 60 mg/m^2
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Severe	5	17	0
Asthenia			
Any	65	44	66
Severe	17	22	0
Diarrhea			
Any	42	28	NA
Severe	6	11	
Stomatitis			
Any	53	67	19
Severe	8	39	1

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline Liver Function: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m^2 dose

NA = not available

In the three-arm monotherapy trial, TAX313, which compared TAXOTERE 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 in advanced breast cancer, grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with TAXOTERE 60 mg/m^2 compared to 55.3% and 65.9% treated with 75 mg/m^2 and 100 mg/m^2, respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m^2 versus 6.9% and 16.5% for patients treated at 75 and 100 mg/m^2, respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m^2 compared to 5.3% and 1.6% for patients treated at 75 mg/m^2 and 100 mg/m^2, respectively.

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m^2, 75 mg/m^2, and 100 mg/m^2, respectively), thrombocytopenia (7%, 11% and 12%, respectively), neutropenia (92%, 94%, and 97% respectively), febrile neutropenia (5%, 7%, and 14%, respectively), treatment-related grade 3/4 infection (2%, 3%, and 7%, respectively) and anemia (87%, 94%, and 97%, respectively).

Combination therapy with TAXOTERE in the adjuvant treatment of breast cancer

The following table presents treatment-emergent adverse reactions observed in 744 patients, who were treated with TAXOTERE 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table 6).

Table 6: Clinically Important Treatment-Emergent Adverse Reactions Regardless of Causal Relationship in Patients Receiving TAXOTERE in Combination with Doxorubicin and Cyclophosphamide (TAX316).

	TAXOTERE 75 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		Fluorouracil 500 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (FAC) n=736 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	92	4	72	2
Neutropenia	71	66	82	49
Fever in absence of infection	47	1	17	0
Infection	39	4	36	2
Thrombocytopenia	39	2	28	1
Febrile neutropenia	25	N/A	3	N/A
Neutropenic infection	12	N/A	6	N/A
Hypersensitivity reactions	13	1	4	0
Lymphedema	4	0	1	0
Fluid Retention*	35	1	15	0
Peripheral edema	27	0	7	0
Weight gain	13	0	9	0
Neuropathy sensory	26	0	10	0
Neuro-cortical	5	1	6	1
Neuropathy motor	4	0	2	0
Neuro-cerebellar	2	0	2	0
Syncope	2	1	1	0
Alopecia	98	N/A	97	N/A
Skin toxicity	27	1	18	0
Nail disorders	19	0	14	0
Nausea	81	5	88	10
Stomatitis	69	7	53	2
Vomiting	45	4	59	7
Diarrhea	35	4	28	2
Constipation	34	1	32	1
Taste perversion	28	1	15	0
Anorexia	22	2	18	1
Abdominal Pain	11	1	5	0
Amenorrhea	62	N/A	52	N/A
Cough	14	0	10	0
Cardiac dysrhythmias	8	0	6	0
Vasodilatation	27	1	21	1
Hypotension	2	0	1	0
Phlebitis	1	0	1	0

	TAXOTERE 75 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		Fluorouracil 500 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (FAC) n=736 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Asthenia	81	11	71	6
Myalgia	27	1	10	0
Arthralgia	19	1	9	0
Lacrimation disorder	11	0	7	0
Conjunctivitis	5	0	7	0

* COSTART term and grading system for events related to treatment.

Of the 744 patients treated with TAC, 36.3% experienced severe treatment-emergent adverse reactions compared to 26.6% of the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1% of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent of patients treated with TAC discontinued treatment due to adverse reactions, compared to 1.1% treated with FAC; fever in the absence of infection and allergy being the most common reasons for withdrawal among TAC-treated patients. Two patients died in each arm within 30 days of their last study treatment; 1 death per arm was attributed to study drugs.

Fever and infection

During the treatment period, fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of TAC and FAC-treated patients, respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients, respectively. There were no septic deaths in either treatment arm during the treatment period.

Gastrointestinal reactions

In addition to gastrointestinal reactions reflected in the table above, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation versus one patient in the FAC arm. Five of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred during the treatment period.

Cardiovascular reactions

More cardiovascular reactions were reported in the TAC arm versus the FAC arm during the treatment period: arrhythmias, all grades (6.2% vs 4.9%), and hypotension, all grades (1.9% vs 0.8%). Twenty-six (26) patients (3.5%) in the TAC arm and 17 patients (2.3%) in the FAC arm developed CHF during the study period. All except one patient in each arm were diagnosed with CHF during the follow-up period. Two (2) patients in TAC arm and 4 patients in FAC arm died due to CHF. The risk of CHF was higher in the TAC arm in the first year, and then was similar in both treatment arms.

Adverse reactions during the follow-up period (median follow-up time of 8 years)

In study TAX316, the most common adverse reactions that started during the treatment period

and persisted into the follow-up period in TAC and FAC patients are described below (median follow-up time of 8 years).

Nervous system disorders

In study TAX316, peripheral sensory neuropathy started during the treatment period and persisted into the follow-up period in 84 patients (11.3%) in TAC arm and 15 patients (2%) in FAC arm. At the end of the follow-up period (median follow-up time of 8 years), peripheral sensory neuropathy was observed to be ongoing in 10 patients (1.3%) in TAC arm, and in 2 patients (0.3%) in FAC arm.

Skin and subcutaneous tissue disorders

In study TAX316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients (92.3%) and 645 of 736 FAC patients (87.6%). At the end of the follow-up period (actual median follow-up time of 8 years), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Reproductive system and breast disorders

In study TAX316, amenorrhea that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 202 of 744 TAC patients (27.2%) and 125 of 736 FAC patients (17.0%). Amenorrhea was observed to be ongoing at the end of the follow-up period (median follow-up time of 8 years) in 121 of 744 TAC patients (16.3%) and 86 FAC patients (11.7%).

General disorders and administration site conditions

In study TAX316, peripheral edema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was observed in 119 of 744 TAC patients (16.0%) and 23 of 736 FAC patients (3.1%). At the end of the follow-up period (actual median follow-up time of 8 years), peripheral edema was ongoing in 19 TAC patients (2.6%) and 4 FAC patients (0.5%).

In study TAX316, lymphedema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 11 of 744 TAC patients (1.5%) and 1 of 736 FAC patients (0.1%). At the end of the follow-up period (actual median follow-up time of 8 years), lymphedema was observed to be ongoing in 6 TAC patients (0.8%) and 1 FAC patient (0.1%).

In study TAX316, asthenia that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 236 of 744 TAC patients (31.7%) and 180 of 736 FAC patients (24.5%). At the end of the follow-up period (actual median follow-up time of 8 years), asthenia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Acute myeloid leukemia (AML)/Myelodysplastic syndrome (MDS)

AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at median follow-up time of 8 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. One TAC patient (0.1%) and 1 FAC patient (0.1%) died due to AML during the follow-up period (median follow-up time of 8 years). Myelodysplastic syndrome occurred in 2 of 744 (0.3%) patients who received TAC and in 1 of

736 (0.1%) patients who received FAC. AML occurs at a higher frequency when these agents are given in combination with radiation therapy.

Lung Cancer

Monotherapy with TAXOTERE for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy

TAXOTERE 75 mg/m^2: Treatment-emergent adverse drug reactions are shown in Table 7. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or where otherwise noted.

Table 7: Treatment-Emergent Adverse Reactions Regardless of Relationship to Treatment in Patients Receiving TAXOTERE as Monotherapy for Non-small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neutropenia			
Any	84	14	83
Grade 3/4	65	12	57
Leukopenia			
Any	84	6	89
Grade 3/4	49	0	43
Thrombocytopenia			
Any	8	0	8
Grade 3/4	3	0	2
Anemia			
Any	91	55	91
Grade 3/4	9	12	14
Febrile Neutropenia**	6	NA†	1
Infection			
Any	34	29	30
Grade 3/4	10	6	9
Treatment Related Mortality	3	NA†	3
Hypersensitivity Reactions			
Any	6	0	1
Grade 3/4	3	0	0
Fluid Retention			
Any	34	ND††	23
Severe	3		3

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neurosensory			
Any	**23**	**14**	**29**
Grade 3/4	**2**	**6**	**5**
Neuromotor			
Any	16	8	10
Grade 3/4	5	6	3
Skin			
Any	20	6	17
Grade 3/4	1	2	1
Gastrointestinal			
Nausea			
Any	34	31	31
Grade 3/4	5	4	8
Vomiting			
Any	22	27	22
Grade 3/4	3	2	6
Diarrhea			
Any	23	6	12
Grade 3/4	3	0	4
Alopecia	56	35	50
Asthenia			
Any	53	57	54
Severe***	18	39	23
Stomatitis			
Any	26	6	8
Grade 3/4	2	0	1
Pulmonary			
Any	41	49	45
Grade 3/4	21	29	19
Nail Disorder			
Any	11	0	2
Severe***	1	0	0
Myalgia			
Any	6	0	3
Severe***	0	0	0
Arthralgia			
Any	3	2	2
Severe***	0	0	1
Taste Perversion			

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Any	6	0	0
Severe***	1	0	0

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN
**Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization
***COSTART term and grading system
†Not Applicable
††Not Done

Combination therapy with TAXOTERE in chemotherapy-naive advanced unresectable or metastatic NSCLC

Table 8 presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Table 8: Adverse Reactions Regardless of Relationship to Treatment in Chemotherapy-Naive Advanced Non-small Cell Lung Cancer Patients Receiving TAXOTERE in Combination with Cisplatin

Adverse Reaction	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
Neutropenia		
Any	91	90
Grade 3/4	74	78
Febrile Neutropenia	5	5
Thrombocytopenia		
Any	15	15
Grade 3/4	3	4
Anemia		
Any	89	94
Grade 3/4	7	25
Infection		
Any	35	37
Grade 3/4	8	8
Fever in absence of infection		
Any	33	29
Grade 3/4	<1	1
Hypersensitivity Reaction*		
Any	12	4
Grade 3/4	3	<1
Fluid Retention**		

Adverse Reaction	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
Any	54	42
All severe or life-threatening events	2	2
Pleural effusion		
Any	23	22
All severe or life-threatening events	2	2
Peripheral edema		
Any	34	18
All severe or life-threatening events	<1	<1
Weight gain		
Any	15	9
All severe or life-threatening events	<1	<1
Neurosensory		
Any	47	42
Grade 3/4	4	4
Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia**		
Any	42	40
All severe or life-threatening events	5	5
Stomatitis		
Any	24	21
Grade 3/4	2	1
Alopecia		
Any	75	42
Grade 3	<1	0
Asthenia**		
Any	74	75
All severe or life-threatening events	12	14
Nail Disorder**		
Any	14	<1
All severe events	<1	0
Myalgia**		

Adverse Reaction	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
Any	18	12
All severe events	<1	<1

*Replaces NCI term "Allergy"
**COSTART term and grading system

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2.0%) in the vinorelbine+cisplatin arm.

The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin (which did not demonstrate a superior survival associated with TAXOTERE *[see Clinical Studies (14.3)]*) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the TAXOTERE+carboplatin arm, while a higher incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Prostate Cancer

Combination therapy with TAXOTERE in patients with prostate cancer

The following data are based on the experience of 332 patients, who were treated with TAXOTERE 75 mg/m^2 every 3 weeks in combination with prednisone 5 mg orally twice daily (see Table 9).

Table 9: Clinically Important Treatment-Emergent Adverse Reactions (Regardless of Relationship) in Patients with Prostate Cancer Who Received TAXOTERE in Combination with Prednisone (TAX327)

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	67	5	58	2
Neutropenia	41	32	48	22
Thrombocytopenia	3	1	8	1
Febrile neutropenia	3	N/A	2	N/A
Infection	32	6	20	4
Epistaxis	6	0	2	0
Allergic Reactions	8	1	1	0
Fluid Retention*	24	1	5	0
Weight Gain*	8	0	3	0

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Peripheral Edema*	18	0	2	0
Neuropathy Sensory	30	2	7	0
Neuropathy Motor	7	2	3	1
Rash/Desquamation	6	0	3	1
Alopecia	65	N/A	13	N/A
Nail Changes	30	0	8	0
Nausea	41	3	36	2
Diarrhea	32	2	10	1
Stomatitis/Pharyngitis	20	1	8	0
Taste Disturbance	18	0	7	0
Vomiting	17	2	14	2
Anorexia	17	1	14	0
Cough	12	0	8	0
Dyspnea	15	3	9	1
Cardiac left ventricular function	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1
Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

Gastric Cancer

Combination therapy with TAXOTERE in gastric adenocarcinoma

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease who were treated with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil (see Table 10).

Table 10: Clinically Important Treatment-Emergent Adverse Reactions Regardless of Relationship to Treatment in the Gastric Cancer Study

	TAXOTERE 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224	
Adverse Reaction	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Anemia	97	18	93	26
Neutropenia	96	82	83	57
Fever in the absence of infection	36	2	23	1
Thrombocytopenia	26	8	39	14
Infection	29	16	23	10
Febrile neutropenia	16	N/A	5	N/A
Neutropenic infection	16	N/A	10	N/A
Allergic reactions	10	2	6	0
Fluid retention*	15	0	4	0
Edema*	13	0	3	0
Lethargy	63	21	58	18
Neurosensory	38	8	25	3
Neuromotor	9	3	8	3
Dizziness	16	5	8	2
Alopecia	67	5	41	1
Rash/itch	12	1	9	0
Nail changes	8	0	0	0
Skin desquamation	2	0	0	0
Nausea	73	16	76	19
Vomiting	67	15	73	19
Anorexia	51	13	54	12
Stomatitis	59	21	61	27
Diarrhea	78	20	50	8
Constipation	25	2	34	3
Esophagitis/dysphagia/odynophagia	16	2	14	5
Gastrointestinal pain/cramping	11	2	7	3
Cardiac dysrhythmias	5	2	2	1
Myocardial ischemia	1	0	3	2
Tearing	8	0	2	0
Altered hearing	6	0	13	2

Clinically important treatment-emergent adverse reactions were determined based upon frequency, severity, and clinical impact of the adverse reaction.
*Related to treatment

Head and Neck Cancer

Combination therapy with TAXOTERE in head and neck cancer

Table 11 summarizes the safety data obtained from patients that received induction

chemotherapy with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil followed by radiotherapy (TAX323; 174 patients) or chemoradiotherapy (TAX324; 251 patients). The treatment regimens are described in Section 14.6.

Table 11: Clinically Important Treatment-Emergent Adverse Reactions (Regardless of Relationship) in Patients with SCCHN Receiving Induction Chemotherapy with TAXOTERE in Combination with Cisplatin and Fluorouracil Followed by Radiotherapy (TAX323) or Chemoradiotherapy (TAX324)

	TAX323 (n=355)				TAX324 (n=494)			
	TAXOTERE arm (n=174)		Comparator arm (n=181)		TAXOTERE arm (n=251)		Comparator arm (n=243)	
Adverse Reaction (by Body System)	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Neutropenia	93	76	87	53	95	84	84	56
Anemia	89	9	88	14	90	12	86	10
Thrombocytopenia	24	5	47	18	28	4	31	11
Infection	27	9	26	8	23	6	28	5
Febrile neutropenia*	5	N/A	2	N/A	12	N/A	7	N/A
Neutropenic infection	14	N/A	8	N/A	12	N/A	8	N/A
Cancer pain	21	5	16	3	17	9	20	11
Lethargy	41	3	38	3	61	5	56	10
Fever in the absence of infection	32	1	37	0	30	4	28	3
Myalgia	10	1	7	0	7	0	7	2
Weight loss	21	1	27	1	14	2	14	2
Allergy	6	0	3	0	2	0	0	0
Fluid retention**	20	0	14	1	13	1	7	2
Edema only	13	0	7	0	12	1	6	1
Weight gain only	6	0	6	0	0	0	1	0
Dizziness	2	0	5	1	16	4	15	2
Neurosensory	18	1	11	1	14	1	14	0
Altered hearing	6	0	10	3	13	1	19	3
Neuromotor	2	1	4	1	9	0	10	2
Alopecia	81	11	43	0	68	4	44	1
Rash/itch	12	0	6	0	20	0	16	1
Dry skin	6	0	2	0	5	0	3	0
Desquamation	4	1	6	0	2	0	5	0
Nausea	47	1	51	7	77	14	80	14
Stomatitis	43	4	47	11	66	21	68	27
Vomiting	26	1	39	5	56	8	63	10
Diarrhea	33	3	24	4	48	7	40	3
Constipation	17	1	16	1	27	1	38	1
Anorexia	16	1	25	3	40	12	34	12

	TAX323 (n=355)				TAX324 (n=494)			
	TAXOTERE arm (n=174)		Comparator arm (n=181)		TAXOTERE arm (n=251)		Comparator arm (n=243)	
Adverse Reaction (by Body System)	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Esophagitis/dysphagia/ Odynophagia	13	1	18	3	25	13	26	10
Taste, sense of smell altered	10	0	5	0	20	0	17	1
Gastrointestinal pain/cramping	8	1	9	1	15	5	10	2
Heartburn	6	0	6	0	13	2	13	1
Gastrointestinal bleeding	4	2	0	0	5	1	2	1
Cardiac dysrhythmia	2	2	2	1	6	3	5	3
Venous* **	3	2	6	2	4	2	5	4
Ischemia myocardial	2	2	1	0	2	1	1	1
Tearing	2	0	1	0	2	0	2	0
Conjunctivitis	1	0	1	0	1	0	0.4	0

Clinically important treatment-emergent adverse reactions based upon frequency, severity, and clinical impact.
*Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.
**Related to treatment.
***Includes superficial and deep vein thrombosis and pulmonary embolism

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon, injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) at the site of previous extravasation.

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction. Ventricular arrhythmia, including ventricular tachycardia, in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide may be associated with fatal outcome.

Cutaneous: cutaneous lupus erythematosus, bullous eruptions such as erythema multiforme and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis, scleroderma-like changes (usually preceded by peripheral lymphedema), severe palmar-plantar erythrodysesthesia, and permanent alopecia.

Gastrointestinal: enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis,

which may be fatal. Abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, intestinal obstruction, ileus, and dehydration as a consequence of gastrointestinal events.

Hearing: ototoxicity, hearing disorders and/or hearing loss, including during use with other ototoxic drugs.

Hematologic: bleeding episodes, disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure.

Hepatic: hepatitis, sometimes fatal, primarily in patients with pre-existing liver disorders.

Hypersensitivity: anaphylactic shock with fatal outcome in patients who received premedication. Severe hypersensitivity reactions with fatal outcome with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and nutrition disorders: electrolyte imbalance, including hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia. Tumor lysis syndrome, sometimes fatal.

Neurologic: confusion, seizures or transient loss of consciousness, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis, cystoid macular edema (CME). Excessive tearing which may be attributable to lacrimal duct obstruction. Transient visual disturbances (flashes, flashing lights, scotomata), typically occurring during drug infusion and reversible upon discontinuation of the infusion, in association with hypersensitivity reactions.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis, which may be fatal. Radiation pneumonitis in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure, the majority of cases were associated with concomitant nephrotoxic drugs.

Second primary malignancies: second primary malignancies, including AML, MDS, NHL, and renal cancer *[see Warnings and Precautions (5.7)]*.

Musculoskeletal disorder: myositis.

7 DRUG INTERACTIONS

Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies and its mechanism of action, TAXOTERE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. TAXOTERE contains alcohol which can interfere with neurobehavioral development *[see Clinical Considerations]*. In animal reproductive studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused an increased incidence of embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively *[see Data]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

TAXOTERE contains alcohol *[see Warnings and Precautions (5.13)]*. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Data

Animal data

Intravenous administration of ≥0.3 and 0.03 mg/kg/day docetaxel to pregnant rats and rabbits, respectively, during the period of organogenesis caused an increased incidence of intrauterine mortality, resorptions, reduced fetal weights, and fetal ossification delays. Maternal toxicity was also observed at these doses, which were approximately 0.02 and 0.003 times the daily maximum recommended human dose based on body surface area, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of docetaxel in human milk, or on its effects on milk production or the breastfed child. No lactation studies in animals have been conducted. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TAXOTERE and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on findings in animals, TAXOTERE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TAXOTERE.

Contraception

Females

Based on genetic toxicity findings, advise females of reproductive potential to use effective contraception during treatment and for 2 months after the last dose of TAXOTERE.

Males

Based on genetic toxicity findings, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of TAXOTERE.

Infertility

Based on findings in animal studies, TAXOTERE may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The alcohol content of TAXOTERE Injection should be taken into account when given to pediatric patients *[see Warnings and Precautions (5.13)]*.

The efficacy of TAXOTERE in pediatric patients as monotherapy or in combination has not been established. The overall safety profile of TAXOTERE in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.

TAXOTERE has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-fluorouracil (TCF).

TAXOTERE Monotherapy

TAXOTERE monotherapy was evaluated in a dose-finding phase 1 trial in 61 pediatric patients (median age 12.5 years, range 1-22 years) with a variety of refractory solid tumors. The recommended dose was 125 mg/m^2 as a 1-hour intravenous infusion every 21 days. The primary dose limiting toxicity was neutropenia.

The recommended dose for TAXOTERE monotherapy was evaluated in a phase 2 single-arm trial in 178 pediatric patients (median age 12 years, range 1-26 years) with a variety of recurrent/refractory solid tumors. Efficacy was not established with tumor response rates ranging from one complete response (CR) (0.6%) in a patient with undifferentiated sarcoma to four partial responses (2.2%) seen in one patient each with Ewing Sarcoma, neuroblastoma, osteosarcoma, and squamous cell carcinoma.

TAXOTERE in Combination

TAXOTERE was studied in combination with cisplatin and 5-fluorouracil (TCF) versus cisplatin and 5-fluorouracil (CF) for the induction treatment of nasopharyngeal carcinoma (NPC) in pediatric patients prior to chemoradiation consolidation. Seventy-five patients (median age 16 years, range 9 to 21 years) were randomized (2:1) to TAXOTERE (75 mg/m^2) in combination with cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2) (TCF) or to cisplatin (80 mg/m^2) and 5-fluorouracil (1000 mg/m^2/day) (CF). The primary endpoint was the CR rate following

induction treatment of NPC. One patient out of 50 in the TCF group (2%) had a complete response while none of the 25 patients in the CF group had a complete response.

Pharmacokinetics

Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2.

Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 μg·h/mL.

In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

Non-small Cell Lung Cancer

In a study conducted in chemotherapy-naive patients with NSCLC (TAX326), 148 patients (36%) in the TAXOTERE+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the TAXOTERE+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI: 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI: 9.3 months, 14 months). In patients 65 years of age or greater treated with TAXOTERE+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with TAXOTERE+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When TAXOTERE was combined with carboplatin for the treatment of chemotherapy-naive, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with TAXOTERE+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Prostate Cancer

Of the 333 patients treated with TAXOTERE every three weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with TAXOTERE every three weeks, the following treatment-emergent adverse reactions occurred at rates ≥10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs 59%), infection (37% vs 24%), nail changes (34% vs 23%), anorexia (21% vs 10%), weight loss (15% vs 5%), respectively.

Breast Cancer

In the adjuvant breast cancer trial (TAX316), TAXOTERE in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

Gastric Cancer

Among the 221 patients treated with TAXOTERE in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in the elderly patients compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Head and Neck Cancer

Among the 174 and 251 patients who received the induction treatment with TAXOTERE in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, 18 (10%) and 32 (13%) of the patients were 65 years of age or older, respectively.

These clinical studies of TAXOTERE in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

8.6 Hepatic Impairment

Avoid TAXOTERE in patients with bilirubin >ULN and patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

The alcohol content of TAXOTERE Injection should be taken into account when given to patients with hepatic impairment *[see Warnings and Precautions (5.13)]*.

10 OVERDOSAGE

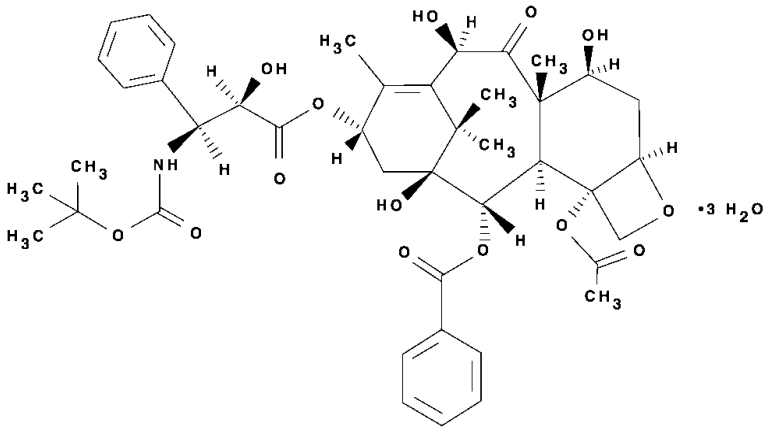
There is no known antidote for TAXOTERE overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single intravenous doses that were ≥154 mg/kg (about 4.5 times the human dose of 100 mg/m^2 on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the human dose of 100 mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m^2 on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

11 DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}•3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

One-vial TAXOTERE (Injection)

TAXOTERE (docetaxel) Injection is a sterile, non-pyrogenic, pale-yellow to brownish-yellow solution at 20 mg/mL concentration.

Each mL contains 20 mg docetaxel (anhydrous) in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol (50% v/v) solution, with citric acid for pH adjustment.

TAXOTERE is available in single-dose vials containing 20 mg (1 mL) or 80 mg (4 mL) docetaxel (anhydrous).

TAXOTERE Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their

disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of docetaxel has been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with initial rapid distribution phase and the late (terminal) phase.

Distribution

Mean steady state volume of distribution was 113 L. Docetaxel is approximately 94% protein bound *in vitro*, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Elimination

With extended plasma sampling up to 8 to 22 days post infusion, the estimated mean total body clearance was 18 L/h/m^2 (range of means: 14 to 23) and mean terminal elimination half-life was 116 hours (range of means: 92 to 135).

Metabolism

Docetaxel is metabolized by the CYP3A4 isoenzyme *in vitro [see Drug Interactions (7)]*.

Excretion

In three cancer patients urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively, within 7 days. About 80% of the radioactivity recovered in feces was excreted during the first 48 hours as 1 major and 3 minor metabolites with less than 8% as unchanged drug.

Specific Populations

Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel was not influenced by age.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients

with combined abnormalities of transaminase and alkaline phosphatase should not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6)]*.

Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

Drug Interaction Studies

Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m^2 intravenous) alone or docetaxel (10 mg/m^2 intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was coadministered with ketoconazole *[see Dosage and Administration (2.7), Drug Interactions (7)]*.

Effect of combination therapies

- Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.
- Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.
- Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.
- Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with metastatic castration-resistant prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.
- Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with docetaxel have not been performed.

Docetaxel was genotoxic by an aneugenic mechanism in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about 1/60th to 1/15th the recommended human dose on a mg/m^2 basis). Docetaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assays.

Docetaxel did not reduce fertility in rats when administered in multiple intravenous doses of up to 0.3 mg/kg (about 1/50th the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at intravenous doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3rd and 1/15th the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

14 CLINICAL STUDIES

14.1 Locally Advanced or Metastatic Breast Cancer

The efficacy and safety of TAXOTERE have been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent–containing regimens or anthracycline-containing regimens).

Randomized Trials

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with TAXOTERE (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). Two hundred three patients were randomized to TAXOTERE and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the TAXOTERE arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results. (See Table 12.)

Table 12: Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously Treated with an Anthracycline-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	**Docetaxel (n=203)**	**Mitomycin/ Vinblastine (n=189)**	**p-value**
Median Survival	11.4 months	8.7 months	
Risk Ratio*, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.73 0.58-0.93		p=0.01 Log Rank
Median Time to Progression	4.3 months	2.5 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.75		p=0.01 Log Rank

Efficacy Parameter	Docetaxel (n=203)	Mitomycin/ Vinblastine (n=189)	p-value
95% CI (Risk Ratio)	0.61-0.94		
Overall Response Rate	28.1%	9.5%	p<0.0001
Complete Response Rate	3.4%	1.6%	Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with TAXOTERE (100 mg/m^2) or doxorubicin (75 mg/m^2) every 3 weeks. One hundred sixty-one patients were randomized to TAXOTERE and 165 patients to doxorubicin. Approximately one-half of patients had received prior chemotherapy for metastatic disease, and one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The study results are summarized below. (See Table 13.)

Table 13: Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously Treated with an Alkylating-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	Docetaxel (n=161)	Doxorubicin (n=165)	p-value
Median Survival	14.7 months	14.3 months	
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		p=0.39 Log Rank
95% CI (Risk Ratio)	0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.93		p=0.45 Log Rank
95% CI (Risk Ratio)	0.71-1.16		
Overall Response Rate	45.3%	29.7%	p=0.004
Complete Response Rate	6.8%	4.2%	Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In another multicenter open-label, randomized trial (TAX313), in the treatment of patients with advanced breast cancer who progressed or relapsed after one prior chemotherapy regimen, 527 patients were randomized to receive TAXOTERE monotherapy 60 mg/m^2 (n=151), 75 mg/m^2 (n=188) or 100 mg/m^2 (n=188). In this trial, 94% of patients had metastatic disease and 79% had received prior anthracycline therapy. Response rate was the primary endpoint. Response rates increased with TAXOTERE dose: 19.9% for the 60 mg/m^2 group compared to 22.3% for the 75 mg/m^2 and 29.8% for the 100 mg/m^2 group; pair-wise comparison between the 60 mg/m^2 and 100 mg/m^2 groups was statistically significant (p=0.037).

Single Arm Studies

TAXOTERE at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall response rate was 37.9% (72/190; 95% CI: 31.0-44.8) and the complete response rate was 2.1%.

TAXOTERE was also studied in three single arm Japanese studies at a dose of 60 mg/m^2, in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% CI: 17.2-55.7), similar to the response rate in single arm studies of 100 mg/m^2.

14.2 Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of TAXOTERE for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either TAXOTERE 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. TAXOTERE was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

Results from a second interim analysis (median follow-up 55 months) are as follows: In study TAX316, the docetaxel-containing combination regimen TAC showed significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0047). The primary endpoint, disease-free survival, included local and distant recurrences, contralateral breast cancer and deaths from any cause. The overall reduction in risk of relapse was 25.7% for TAC-treated patients. (See Figure 1.)

At the time of this interim analysis, based on 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90). (See Figure 2.) There will be further analysis at the time survival data mature.

Figure 1: TAX316 Disease Free Survival K-M curve

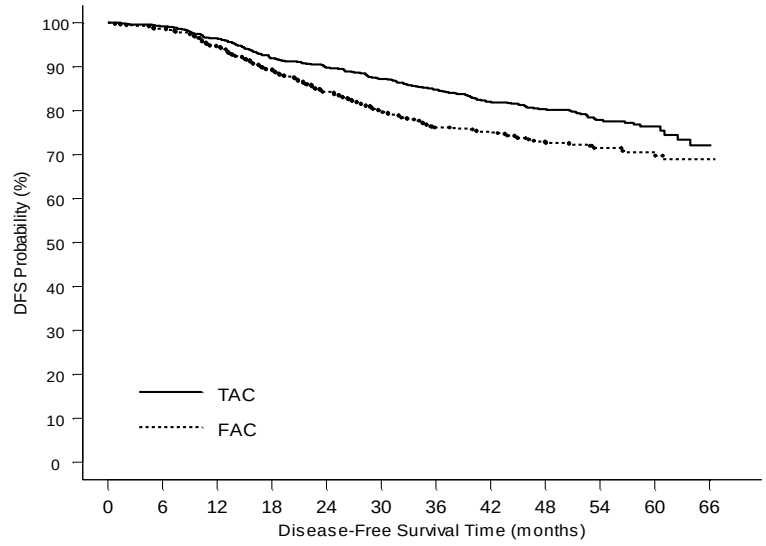
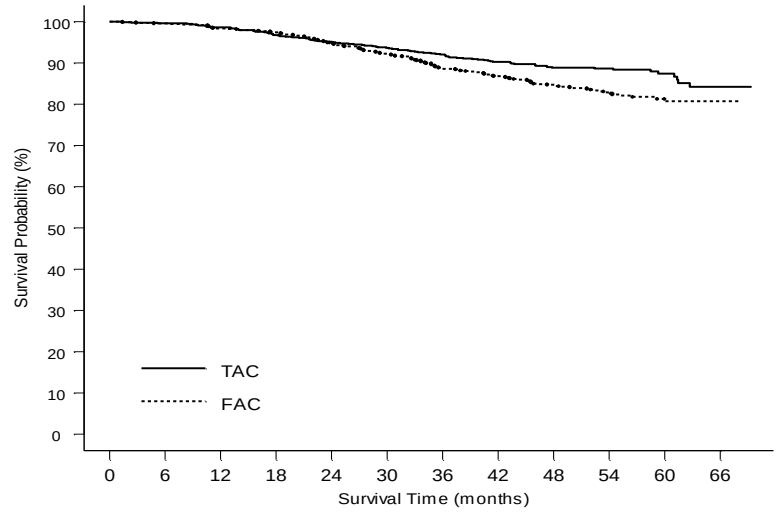


Figure 2: TAX316 Overall Survival K-M Curve



The following table describes the results of subgroup analyses for DFS and OS (See Table 14).

Table 14: Subset Analyses-Adjuvant Breast Cancer Study

Patient subset	Number of patients	Disease Free Survival		Overall Survival	
		Hazard ratio*	95% CI	Hazard ratio*	95% CI
No. of positive nodes					
Overall	744	0.74	(0.60, 0.92)	0.69	(0.53, 0.90)
1-3	467	0.64	(0.47, 0.87)	0.45	(0.29, 0.70)
4+	277	0.84	(0.63, 1.12)	0.93	(0.66, 1.32)
Receptor status					
Positive	566	0.76	(0.59, 0.98)	0.69	(0.48, 0.99)

Negative	178	0.68	(0.48, 0.97)	0.66	(0.44, 0.98)

* a hazard ratio of less than 1 indicates that TAC is associated with a longer disease free survival or overall survival compared to FAC.

14.3 Non-small Cell Lung Cancer (NSCLC)

The efficacy and safety of TAXOTERE has been evaluated in patients with unresectable, locally advanced or metastatic non-small cell lung cancer whose disease has failed prior platinum-based chemotherapy or in patients who are chemotherapy naive.

Monotherapy with TAXOTERE for NSCLC Previously Treated with Platinum-Based Chemotherapy

Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5.3)]*.

One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an ECOG performance status ≤2 to TAXOTERE or best supportive care. The primary endpoint of the study was survival. Patients were initially randomized to TAXOTERE 100 mg/m^2 or best supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE 75 mg/m^2. A total of 104 patients were randomized in this amended study to either TAXOTERE 75 mg/m^2 or best supportive care.

In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG performance status ≤2 were randomized to TAXOTERE 75 mg/m^2, TAXOTERE 100 mg/m^2 and a treatment in which the investigator chose either vinorelbine 30 mg/m^2 days 1, 8, and 15 repeated every 3 weeks or ifosfamide 2 g/m^2 days 1-3 repeated every 3 weeks. Forty percent of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was survival in both trials. The efficacy data for the TAXOTERE 75 mg/m^2 arm and the comparator arms are summarized in Table 15 and Figures 3 and 4 showing the survival curves for the two studies.

Table 15: Efficacy of TAXOTERE in the Treatment of Non-small Cell Lung Cancer Patients Previously Treated with a Platinum-Based Chemotherapy Regimen (Intent-to-Treat Analysis)

	TAX317		**TAX320**	
	Docetaxel 75 mg/m^2 n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m^2 n=125**	**Control (V/I*) n=123**
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio†† , Mortality (Docetaxel: Control)	0.56		0.82	

	TAX317		TAX320	
	Docetaxel 75 mg/m^2 n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m^2 n=125**	**Control (V/I*) n=123**
95% CI (Risk Ratio)	(0.35, 0.88)		(0.63, 1.06)	
Median Survival 95% CI	7.5 months** (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)
% 1-year Survival 95% CI	37%**† (24, 50)	12% (2, 23)	30%**† (22, 39)	20% (13, 27)
Time to Progression 95% CI	12.3 weeks** (9.0, 18.3)	7.0 weeks (6.0, 9.3)	8.3 weeks (7.0, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate 95% CI	5.5% (1.1, 15.1)	Not Applicable	5.7% (2.3, 11.3)	0.8% (0.0, 4.5)

*Vinorelbine/Ifosfamide
**p≤0.05
†uncorrected for multiple comparisons
††a value less than 1.00 favors docetaxel

Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint; that trial also showed an increased rate of survival to one year. In the second study (TAX320) the rate of survival at one year favored TAXOTERE 75 mg/m^2.

Figure 3: TAX317 Survival K-M Curves - TAXOTERE 75 mg/m^2 Versus Best Supportive Care

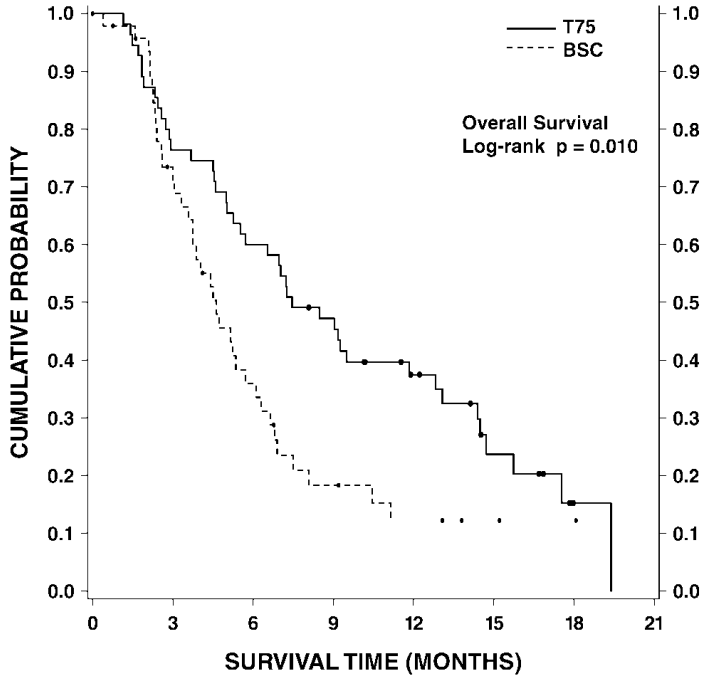
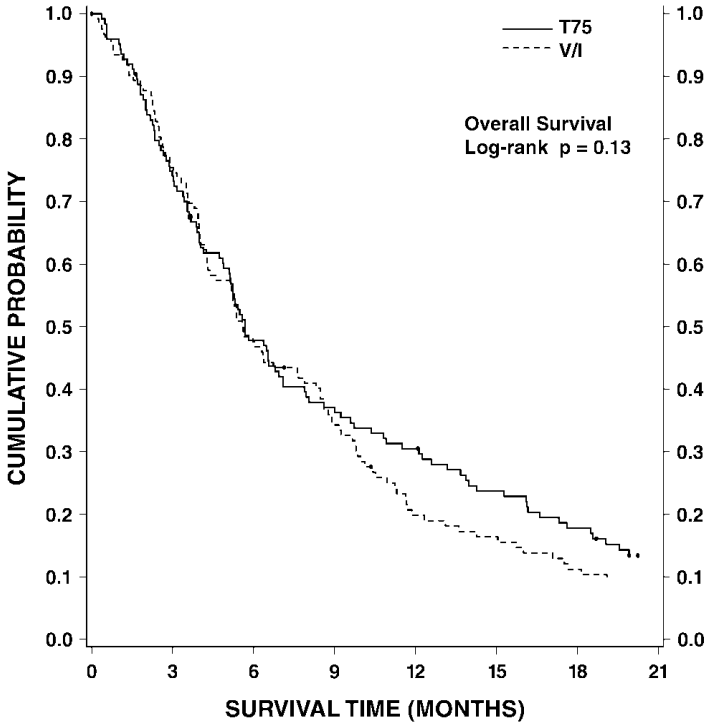


Figure 4: TAX320 Survival K-M Curves - TAXOTERE 75 mg/m^2 Versus Vinorelbine or Ifosfamide Control



Patients treated with TAXOTERE at a dose of 75 mg/m^2 experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

Combination Therapy with TAXOTERE for Chemotherapy-Naive NSCLC

In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments: TAXOTERE 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks; vinorelbine 25 mg/m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks; or a combination of TAXOTERE and carboplatin.

The primary efficacy endpoint was overall survival. Treatment with TAXOTERE+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of TAXOTERE to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the TAXOTERE+cisplatin arm and the comparator arm are summarized in Table 16.

Table 16: Survival Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naive NSCLC

Comparison	TAXOTERE + Cisplatin n=408	Vinorelbine + Cisplatin n=405

Kaplan-Meier Estimate of Median Survival	10.9 months	10.0 months
p-value[a]	0.122	
Estimated Hazard Ratio[b]	0.88	
Adjusted 95% CI[c]	(0.74, 1.06)	

[a] From the superiority test (stratified log rank) comparing TAXOTERE+cisplatin to vinorelbine+cisplatin
[b]Hazard ratio of TAXOTERE+cisplatin versus vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that TAXOTERE+cisplatin is associated with a longer survival.
[c]Adjusted for interim analysis and multiple comparisons.

The second comparison in the same three-arm study, vinorelbine+cisplatin versus TAXOTERE+carboplatin, did not demonstrate superior survival associated with the TAXOTERE arm (Kaplan-Meier estimate of median survival was 9.1 months for TAXOTERE+carboplatin compared to 10.0 months on the vinorelbine+cisplatin arm) and the TAXOTERE+carboplatin arm did not demonstrate preservation of at least 50% of the survival effect of vinorelbine added to cisplatin. Secondary endpoints evaluated in the trial included objective response and time to progression. There was no statistically significant difference between TAXOTERE+cisplatin and vinorelbine+cisplatin with respect to objective response and time to progression (see Table 17).

Table 17: Response and TTP Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naive NSCLC

Endpoint	TAXOTERE + Cisplatin	Vinorelbine + Cisplatin	p-value
Objective Response Rate (95% CI)[a]	31.6% (26.5%, 36.8%)	24.4% (19.8%, 29.2%)	Not Significant
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a]Adjusted for multiple comparisons.
[b]Kaplan-Meier estimates.

14.4 Castration-Resistant Prostate Cancer

The safety and efficacy of TAXOTERE in combination with prednisone in patients with metastatic castration-resistant prostate cancer were evaluated in a randomized multicenter active control trial. A total of 1006 patients with Karnofsky Performance Status (KPS) ≥60 were randomized to the following treatment groups:

- TAXOTERE 75 mg/m^2 every 3 weeks for 10 cycles.
- TAXOTERE 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles.
- Mitoxantrone 12 mg/m^2 every 3 weeks for 10 cycles.

All 3 regimens were administered in combination with prednisone 5 mg twice daily, continuously.

In the TAXOTERE every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the TAXOTERE weekly arm, no overall

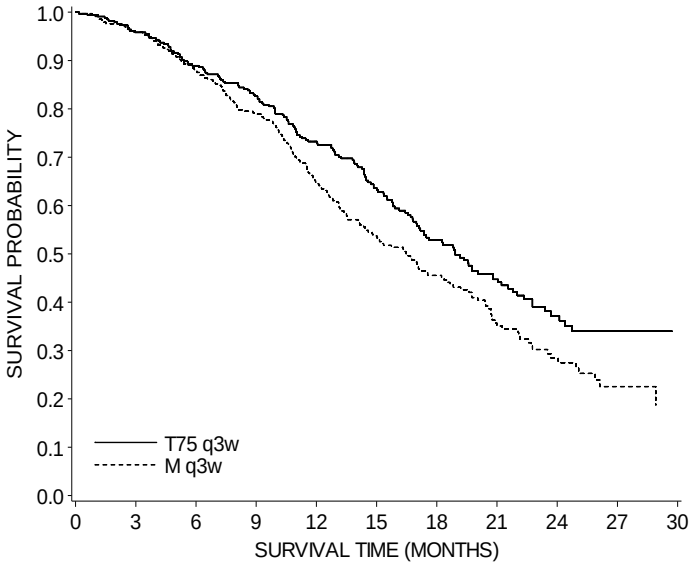
survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the TAXOTERE every 3 week arm versus the control arm are summarized in Table 18 and Figure 5.

Table 18: Efficacy of TAXOTERE in the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (Intent-to-Treat Analysis)

	TAXOTERE + Prednisone every 3 weeks	Mitoxantrone + Prednisone every 3 weeks
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	--
95% CI	(0.619-0.936)	--
p-value*	0.0094	--

*Stratified log-rank test. Threshold for statistical significance = 0.0175 because of 3 arms.

Figure 5: TAX327 Survival K-M Curves



14.5 Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of TAXOTERE for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS >70 were treated with either TAXOTERE (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary

endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 19 and Figures 6 and 7.

Table 19: Efficacy of TAXOTERE in the Treatment of Patients with Gastric Adenocarcinoma

Endpoint	**TCF n=221**	**CF n=224**
Median TTP (months)	5.6	3.7
(95% CI)	(4.86-5.91)	(3.45-4.47)
Hazard ratio†	0.68	
(95% CI)	(0.55-0.84)	
*p-value	0.0004	
Median survival (months)	9.2	8.6
(95% CI)	(8.38-10.58)	(7.16-9.46)
Hazard ratio†	0.77	
(95% CI)	(0.62-0.96)	
*p-value	0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified log-rank test
†For the hazard ratio (TCF/CF), values less than 1.00 favor the TAXOTERE arm.

Subgroup analyses were consistent with the overall results across age, gender and race.

Figure 6: Gastric Cancer Study (TAX325) Time to Progression K-M Curve

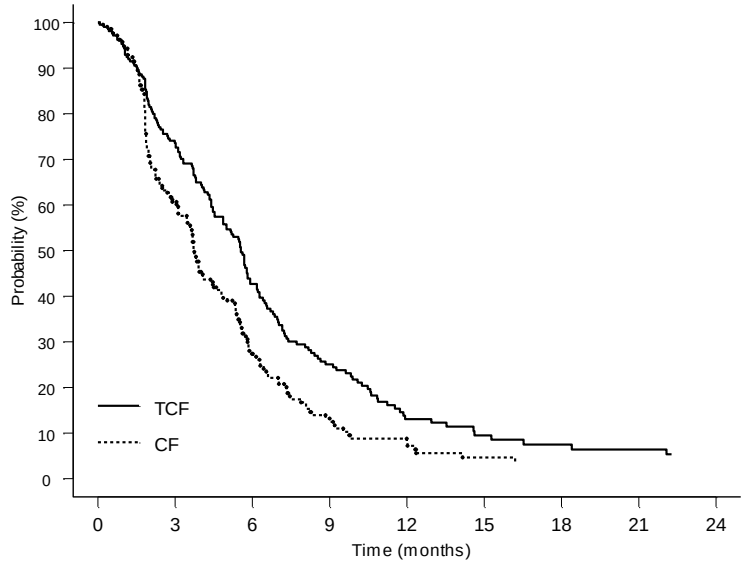
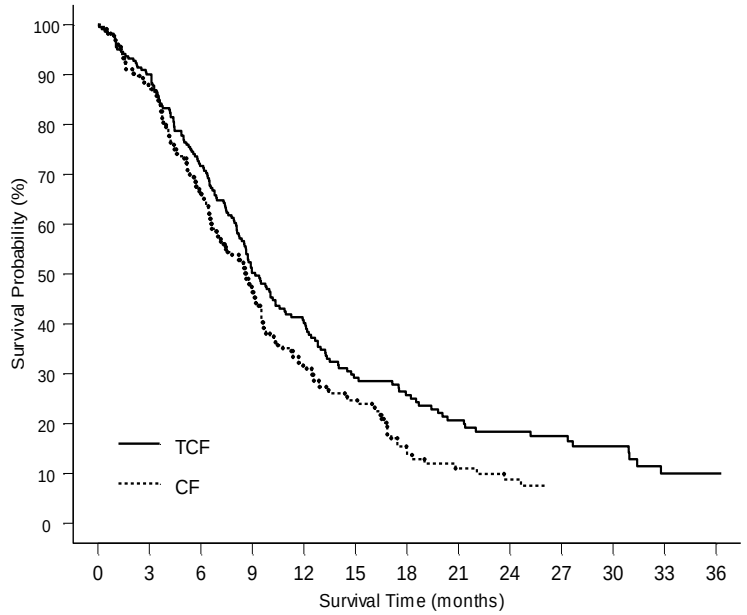


Figure 7: Gastric Cancer Study (TAX325) Survival K-M Curve



14.6 Head and Neck Cancer

Induction Chemotherapy Followed by Radiotherapy (TAX323)

The safety and efficacy of TAXOTERE in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the TAXOTERE arm received TAXOTERE (T) 75 mg/m^2 followed by cisplatin (P) 75 mg/m^2 on Day 1, followed by fluorouracil (F) 750 mg/m^2 per day as a continuous infusion on

Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m^2 on Day 1, followed by fluorouracil (F) 1000 mg/m^2/day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was delivered either with a conventional fraction regimen (1.8 Gy-2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy) or with an accelerated/hyperfractionated regimen (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week, for a total dose of 70 to 74 Gy, respectively). Surgical resection was allowed following chemotherapy, before or after radiotherapy.

The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs 8.3 months, respectively) with an overall median follow-up time of 33.7 months. Median overall survival with a median follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs 14.2 months, respectively). Efficacy results are presented in Table 20 and Figures 8 and 9.

Table 20: Efficacy of TAXOTERE in the Induction Treatment of Patients with Inoperable Locally Advanced SCCHN (Intent-to-Treat Analysis)

Endpoint	**TAXOTERE + Cisplatin + Fluorouracil n=177**	**Cisplatin + Fluorouracil n=181**
Median progression free survival (months) (95% CI)	11.4 (10.1-14.0)	8.3 (7.4-9.1)
Adjusted Hazard ratio (95% CI) *p-value	0.71 (0.56-0.91) 0.0077	
Median survival (months) (95% CI)	18.6 (15.7-24.0)	14.2 (11.5-18.7)
Hazard ratio (95% CI) **p-value	0.71 (0.56-0.90) 0.0055	
Best overall response (CR + PR) to chemotherapy (%) (95% CI)	67.8 (60.4-74.6)	53.6 (46.0-61.0)
***p-value	0.006	
Best overall response (CR + PR) to study treatment [chemotherapy +/- radiotherapy] (%) (95% CI)	72.3 (65.1-78.8)	58.6 (51.0-65.8)
***p-value	0.006	

A Hazard ratio of less than 1 favors TAXOTERE+cisplatin+fluorouracil
*Stratified log-rank test based on primary tumor site
**Stratified log-rank test, not adjusted for multiple comparisons
***Chi square test, not adjusted for multiple comparisons

Figure 8: TAX323 Progression-Free Survival K-M Curve

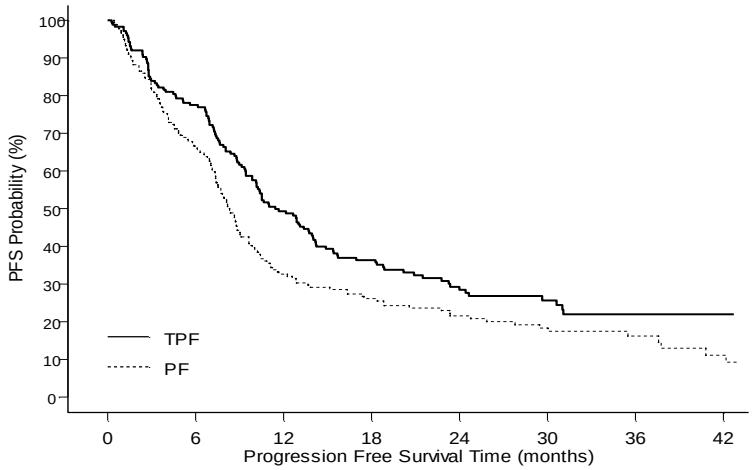
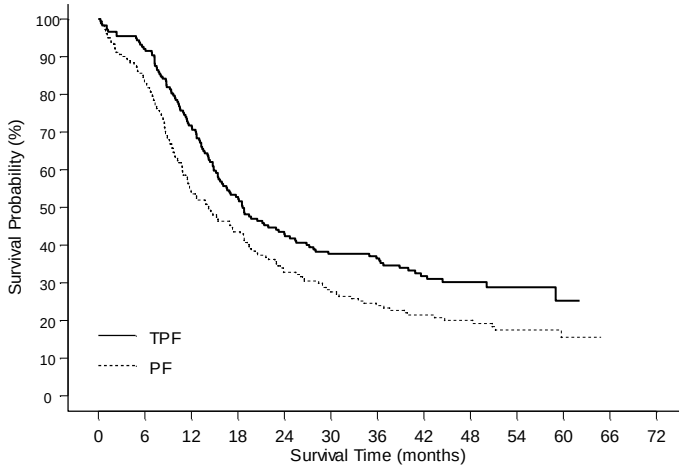


Figure 9: TAX323 Overall Survival K-M Curve



Induction Chemotherapy Followed by Chemoradiotherapy (TAX324)

The safety and efficacy of TAXOTERE in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomized, multicenter open-label trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two treatment arms. Patients on the TAXOTERE arm received TAXOTERE (T) 75 mg/m^2 by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m^2 administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m^2/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. Patients on the comparator arm received cisplatin (P) 100 mg/m^2 as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m^2/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles.

All patients in both treatment arms who did not have progressive disease were to receive 7 weeks of chemoradiotherapy (CRT) following induction chemotherapy 3 to 8 weeks after the start of the last cycle. During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks for a total dose of 70-72 Gy). Surgery on the primary site of disease and/or neck could be considered at any time following completion of CRT.

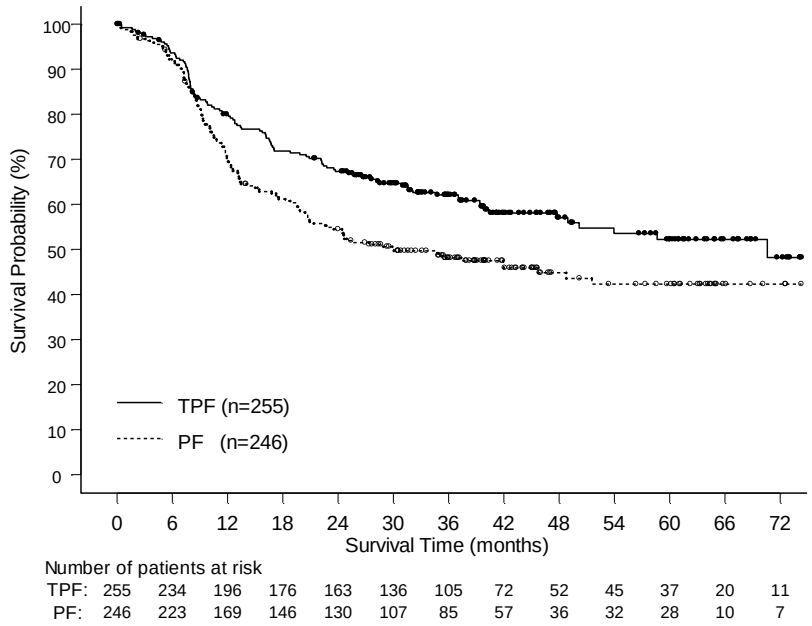
The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, p=0.0058) with the TAXOTERE-containing regimen compared to PF (median OS: 70.6 vs 30.1 months, respectively, hazard ratio [HR]=0.70, 95% confidence interval [CI]=0.54-0.90). Overall survival results are presented in Table 21 and Figure 10.

Table 21: Efficacy of TAXOTERE in the Induction Treatment of Patients with Locally Advanced SCCHN (Intent-to-Treat Analysis)

Endpoint	**TAXOTERE + Cisplatin + Fluorouracil n=255**	**Cisplatin + Fluorouracil n=246**
Median overall survival (months) (95% CI)	70.6 (49.0-NE)	30.1 (20.9-51.5)
Hazard ratio: (95% CI) *p-value	0.70 (0.54-0.90) 0.0058	

A Hazard ratio of less than 1 favors TAXOTERE+cisplatin+fluorouracil
*unadjusted log-rank test
NE - not estimable

Figure 10: TAX324 Overall Survival K-M Curve



15 REFERENCES

1. "OSHA Hazardous Drugs." http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

One-vial TAXOTERE (Injection)

TAXOTERE Injection is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous solution. Discard unused portion.

TAXOTERE 20 mg/mL (NDC 0075-8003-01)

TAXOTERE (docetaxel) Injection 20 mg/1 mL: 20 mg docetaxel in 1 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

The vial is in a blister pack in one carton.

TAXOTERE 80 mg/4 mL (NDC 0075-8004-04)

TAXOTERE (docetaxel) Injection 80 mg/4 mL: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

The vial is in a blister pack in one carton.

16.2 Storage

Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from light. Freezing does not adversely affect the product.

16.3 Handling and Disposal

TAXOTERE is a hazardous drug. Follow applicable special handling and disposal procedures.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Bone Marrow Suppression

Advise patients that periodic assessment of their blood count will be performed to detect neutropenia, thrombocytopenia, and/ or anemia *[see Contraindications (4), Warnings and Precautions (5.3)]*. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.

Enterocolitis and Neutropenic Colitis

Advise patients of the symptoms of colitis, such as abdominal pain or tenderness, and/or diarrhea, with or without fever, and instruct patients to promptly contact their healthcare provider if they experience these symptoms *[see Dosage and Administration (2.7) and Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Ask patients whether they have previously received paclitaxel therapy, and if they have experienced a hypersensitivity reaction to paclitaxel. Instruct patients to immediately report to

their healthcare provider signs of a hypersensitivity reaction *[see Contraindications (4), Warnings and Precautions (5.5)]*.

Fluid Retention

Advise patients to report signs of fluid retention such as peripheral edema in the lower extremities, weight gain, and dyspnea immediately to their healthcare provider *[see Warnings and Precautions (5.6)]*.

Second Primary Malignancies

Advise patients on the risk of second primary malignancies during treatment with TAXOTERE *[see Warnings and Precautions (5.7)]*.

Cutaneous Reactions

Advise patients that localized erythema of the extremities and severe skin toxicities may occur. Instruct patients to immediately report severe cutaneous reactions to their healthcare provider *[see Dosage and Administration (2.7) and Warnings and Precautions (5.8)]*.

Neurologic Reactions

Advise patients that neurosensory symptoms or peripheral neuropathy may occur. Instruct patients to immediately report neurologic reactions to their healthcare provider *[see Dosage and Administration (2.7) and Warnings and Precautions (5.9)]*.

Eye Disorders

Advise patients that vision disturbances and excessive tearing are associated with TAXOTERE administration. Instruct patients to immediately report any vision changes to their healthcare provider *[see Warnings and Precautions (5.10)]*.

Gastrointestinal Reactions

Explain to patients that nausea, vomiting, diarrhea, and constipation are associated with TAXOTERE administration. Instruct patients to report any severe events to their healthcare provider *[see Adverse Reactions (6)]*.

Cardiac Disorders

Advise patients to report any irregular and/or rapid heartbeat, severe shortness of breath, dizziness, and/or fainting immediately to their healthcare provider *[see Adverse Reactions (6)]*.

Other Common Adverse Reactions

Advise patients that other common adverse reactions associated with TAXOTERE may include alopecia (cases of permanent hair loss have been reported), asthenia, anorexia, dysgeusia, mucositis, myalgia, nail disorders, or pain. Instruct patients to report these reactions to their healthcare provider if serious events occur *[see Adverse Reactions (6)]*.

Importance of Corticosteroids

Explain the significance of oral corticosteroids such as dexamethasone administration to the patient to help facilitate compliance. Instruct patients to report to their healthcare provider if they were not compliant with the oral corticosteroid regimen *[see Dosage and Administration (2.6)]*.

Embryo-Fetal Toxicity

TAXOTERE can cause fetal harm. Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise patients to avoid becoming pregnant while receiving this drug. Advise female patients of reproductive potential to use effective contraceptives during treatment and for 2 months after the last dose of TAXOTERE. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of TAXOTERE *[see Warnings and Precautions (5.12), and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during TAXOTERE treatment and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that TAXOTERE may impair fertility *[see Nonclinical Toxicology (13.1)]*.

Alcohol Content in TAXOTERE

Explain to patients the possible effects of the alcohol content in TAXOTERE, including possible effects on the central nervous system *[see Warnings and Precautions (5.13)]*.

Tumor Lysis Syndrome

Advise patients of the potential risk of tumor lysis syndrome and to immediately report any signs or symptoms associated with this event (nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, reduced amount of urine, unusual tiredness, muscle cramps) to their healthcare provider. Advise patients of the importance of keeping scheduled appointment for blood work or other laboratory tests and of drinking adequate fluids to avoid dehydration. *[see Warnings and Precautions (5.14)]*.

Ability to Drive or Operate Machines

Explain to patients that TAXOTERE may impair their ability to drive or operate machines due to its side effects *[see Adverse Reactions (6)]* or due to the alcohol content of TAXOTERE *[see Warnings and Precautions (5.13)]*. Advise them not to drive or use machines if they experience these side effects during treatment.

Drug Interactions

Inform patients about the risk of drug interactions and the importance of providing a list of prescription and non-prescription drugs to their healthcare provider *[see Drug Interactions (7)]*.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

Patient Information
TAXOTERE (TAX-O-TEER)
(docetaxel) injection
for intravenous use

What is the most important information I should know about TAXOTERE?
TAXOTERE can cause serious side effects, including death.

- **The chance of death in people who receive TAXOTERE is higher if you:**
  - have liver problems
  - receive high doses of TAXOTERE
  - have non-small cell lung cancer and have been treated with chemotherapy medicines that contain platinum
- **TAXOTERE can affect your blood cells.** Your healthcare provider should do routine blood tests during treatment with TAXOTERE. This will include regular checks of your white blood cell counts. If your white blood cells are too low, your healthcare provider may not treat you with TAXOTERE until you have enough white blood cells. People with low white blood cell counts can develop life-threatening infections. The earliest sign of infection may be fever. Follow your healthcare provider's instructions for how often to take your temperature during treatment with TAXOTERE. Call your healthcare provider right away if you have a fever.
- **Swelling (inflammation) of the small intestine and colon.** This can happen at any time during treatment and could lead to death as early as the first day you get symptoms. Tell your healthcare provider right away if you develop new or worse symptoms of intestinal problems, including stomach (abdominal) pain or tenderness or diarrhea, with or without fever.
- **Severe allergic reactions** are medical emergencies that can happen in people who receive TAXOTERE and can lead to death. You may be at higher risk of developing a severe allergic reaction to TAXOTERE if you are allergic to paclitaxel. Your healthcare provider will monitor you closely for allergic reactions during your TAXOTERE infusion.

  Tell your healthcare provider right away if you have any of these signs of a severe allergic reaction:
  - trouble breathing
  - sudden swelling of your face, lips, tongue, throat, or trouble swallowing
  - hives (raised bumps), rash, or redness all over your body
- **Your body may hold too much fluid (severe fluid retention)** during treatment with TAXOTERE. This can be life threatening. To decrease the chance of this happening, you must take another medicine, a corticosteroid, before each TAXOTERE treatment. You must take the corticosteroid exactly as your healthcare provider tells you. Tell your healthcare provider or nurse before your TAXOTERE treatment if you forgot to take your corticosteroid dose or do not take it as your healthcare provider tells you. Tell your healthcare provider right away if you have swelling in your legs or feet, weight gain or shortness of breath.
- **Risk of new cancers.** An increase in new (second) cancers has happened in people treated with TAXOTERE together with certain other anticancer treatments. This includes certain blood cancers, such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), non-Hodgkin's Lymphoma (NHL), and kidney cancer.
  - Changes in blood counts due to leukemia and other blood disorders may occur years after treatment with TAXOTERE.

  Your healthcare provider will check you for new cancers during and after your treatment with TAXOTERE.
- **Severe skin problems.**

  Tell your healthcare provider right away if you have any of these signs of a severe skin reaction:
  - redness and swelling of your arms and legs.
  - blistering, peeling, or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genitals, hands or feet) with or without a rash. You may also have flu-like symptoms such as fever, chills, or muscle aches.
  - red, scaly rash all over your body with blisters, small red or white bumps under the skin that contain pus (pustules), and fever.

What is TAXOTERE?

TAXOTERE is a prescription anticancer medicine used to treat certain people with:

- breast cancer
- non-small cell lung cancer
- prostate cancer
- stomach cancer
- head and neck cancer

It is not known if TAXOTERE is effective in children.

Do not receive TAXOTERE if you:

- have a low white blood cell count.
- have had a severe allergic reaction to:
  - docetaxel, the active ingredient in TAXOTERE, or
  - any other medicines that contain polysorbate 80. Ask your healthcare provider or pharmacist if you are not sure.

See "**What is the most important information I should know about TAXOTERE?**" for the signs and symptoms of a severe allergic reaction.

See the end of this Patient Information for a complete list of the ingredients in TAXOTERE.

Before you receive TAXOTERE, tell your healthcare provider about all of your medical conditions, including if you:

- are allergic to any medicines, including paclitaxel. See "**Do not receive TAXOTERE if you**".
- have liver problems
- have kidney problems
- are pregnant or plan to become pregnant. TAXOTERE can harm your unborn baby. You should not become pregnant during treatment with TAXOTERE. Tell your healthcare provider if you become pregnant or you think you may be pregnant during treatment with TAXOTERE.

  Females who are able to become pregnant:
  - Your healthcare provider will check to see if you are pregnant before you start treatment with TAXOTERE.
  - You should use effective birth control (contraception) during treatment with TAXOTERE and for 2 months after the last dose.

  Males with female partners who are able to become pregnant should use effective birth control during treatment with TAXOTERE and for 4 months after the last dose.

  Talk to your healthcare provider if you have questions about birth control options that are right for you.
- are breastfeeding or plan to breastfeed. It is not known if TAXOTERE passes into your breast milk. Do not breastfeed during treatment with TAXOTERE and for 1 week after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TAXOTERE may affect the way other medicines work, and other medicines may affect the way TAXOTERE works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive TAXOTERE?

- TAXOTERE will be given to you as an intravenous (IV) injection into your vein, usually over 1 hour.
- TAXOTERE is usually given every 3 weeks.
- Your healthcare provider will decide how long you will receive treatment with TAXOTERE.
- Your healthcare provider will check your blood cell counts and other blood tests during your treatment with TAXOTERE to check for side effects of TAXOTERE.
- Your healthcare provider may stop your treatment, change the timing of your treatment, or change the dose of your treatment if you have certain side effects while receiving TAXOTERE.

What are the possible side effects of TAXOTERE?

TAXOTERE may cause serious side effects including death.

- See **"What is the most important information I should know about TAXOTERE?"**
- **Neurologic problems.** Neurologic symptoms are common in people who receive TAXOTERE but can be severe. Tell your healthcare provider right away if you have numbness, tingling, or burning in your hands or feet (peripheral neuropathy) or weakness of your legs, feet, arms, or hands (motor weakness).
- **Vision problems** including blurred vision or loss of vision. Tell your healthcare provider right away if you have any vision changes.
- **TAXOTERE injection contains alcohol.** The alcohol content in TAXOTERE may impair your ability to drive or use machinery right after receiving TAXOTERE. Consider whether you should drive, operate machinery or do other dangerous activities right after you receive TAXOTERE treatment.
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure, the need for dialysis treatment, or heart problems, and may lead to death. Your healthcare provider will do blood tests to check for TLS when you first start treatment and during treatment with TAXOTERE. Tell your healthcare provider right away if you have any symptoms of TLS during treatment with TAXOTERE, including:
  - nausea
  - vomiting
  - confusion
  - shortness of breath
  - irregular heartbeat
  - dark or cloudy urine
  - reduced amount of urine
  - unusual tiredness
  - muscle cramps
- You may experience side effects of this medicine that may impair your ability to drive, use tools, or operate machines. If this happens, do not drive or use any tools or machines before discussing with your healthcare provider.

The most common side effects of TAXOTERE include:

- infections
- low white blood cells (help fight infections), low red blood cells (anemia) and low platelets (help blood to clot)
- allergic reactions (See **"What is the most important information I should know about TAXOTERE?"**)
- changes in your sense of taste
- shortness of breath
- constipation
- decreased appetite
- changes in your fingernails or toenails
- swelling of your hands, face or feet
- feeling weak or tired
- joint and muscle pain
- nausea and vomiting
- diarrhea
- mouth or lip sores
- hair loss: in some people, permanent hair loss has been reported
- redness of the eye, excess tearing
- skin reactions at the site of TAXOTERE administration such as increased skin pigmentation, redness, tenderness, swelling, warmth or dryness of the skin
- tissue damage if TAXOTERE leaks out of the vein into the tissues

Tell your healthcare provider if you have a fast or irregular heartbeat, severe shortness of breath, dizziness or fainting during your infusion. If any of these events occurs after your infusion, get medical help right away.

TAXOTERE may affect fertility in males. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of TAXOTERE. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TAXOTERE.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information. You can ask your pharmacist or healthcare provider for information about TAXOTERE that is written for health professionals.

What are the ingredients in TAXOTERE?

Active ingredient: docetaxel
Inactive ingredients: polysorbate 80 and dehydrated alcohol solution, with citric acid for pH adjustment.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

For more information, call 1-800-633-1610 or go to www.sanofi-aventis.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: January 2023

Every three-week injection of TAXOTERE for breast, non-small cell lung and stomach, and head and neck cancers
Take your oral corticosteroid medicine as your healthcare provider tells you.

Oral corticosteroid dosing:

Day 1 Date:_____ Time: _____ AM _____ PM

Day 2 Date:_____ Time: _____ AM _____ PM
(TAXOTERE Treatment Day)

Day 3 Date:_____ Time: _____ AM _____ PM

Every three-week injection of TAXOTERE for prostate cancer
Take your oral corticosteroid medicine as your healthcare provider tells you.

Oral corticosteroid dosing:

Date: _____ Time:_____

Date: _____ Time:_____
(TAXOTERE Treatment Day)
Time:_____

EXHIBIT K

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	§ MDL No. 2740 § § SECTION: "N" (5)
This Document Relates To: ALL CASES	§ § JUDGE ENGELHARDT § § MAG. JUDGE NORTH

- - -

Friday, March 23, 2018

- - -

Videotaped deposition of PIERRE MANCINI, held at DLA Piper UK LLP, 3 Noble Street, London, United Kingdom, commencing at 8:19 a.m., on the above date, before Susan D. Wasilewski, Registered Professional Reporter, Certified Realtime Reporter, Certified Realtime Captioner, Certified Manager of Reporting Services, Florida Professional Reporter, Certified Court Reporter (NJ), and Realtime Systems Administrator

- - -

GOLKOW LITIGATION SERVICES
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

correct?

A. Exactly.

Q. But you don't do that on a daily basis; you have people within your department that do that for you?

A. Yes.

Q. So if you wanted to, you could go to a person within your department and say, let's pull up the data sets from TAX316, and you would be able to do that by going to the WISE system?

MR. McCULLY: Object to form.

Q. Correct?

MR. McCULLY: Sorry. Object to form.

A. Yeah. If we have a table to generate, we can, you know, assign a statistician and a programmer and ask them to generate that.

Q. But if you wanted to see the data sets that were already generated for, say, a clinical study report, you could go find those on WISE as well?

A. Yes.

Q. And you could find the SAS data programs on WISE as well?

A. Of course.

Q. Okay. Have you ever had to look at those yourself?

Q. -- of 250?
A. Oh, no. Yeah, you're right.
Q. 10?
A. Sorry, sorry. I'm --
Q. That's okay.
A. Yeah. We have many numbers, a lot of things.
Q. So we have 10 people out of 251 in Study TAX324 that have Grade 3/4 -- or excuse me -- that are reflected in this document as having alopecia (G3/4, 4 percent), which is 10 individuals; whereas, in the pooled analysis that you did, you had 1,276 individuals, yet one -- only one person had G3/4, or 0.1 percent had Grade 3/4 alopecia.
MR. McCULLY: Object to form. Is there --
A. I --
MR. McCULLY: Do you have a question?
MR. MICELI: Yeah.
Q. That's -- is that a correct statement?
MR. McCULLY: Thank you.
A. Okay. Yes, this is a correct statement.
Q. Okay. Did you, in doing your statistical analysis, your pooled analysis of GEICAM and TAX316, did you do any follow-up investigation into how the adverse events were collected?

A. This is not in my scope of responsibilities. I'm analyzing data --

Q. And that's --

A. -- which are -- which are -- which are validated and clean. I'm not in charge of doing the follow-up.

Q. When you say "validated and clean," would -- do you mean by that that the data that you receive and you operate upon is data that has been provided to you from clinical trials that you believe to be validated and accurate?

A. Yes.

Q. Okay. We'll talk about that in due course of this deposition.

MR. MICELI: We've been going for about another hour, I think, haven't we?

THE VIDEOGRAPHER: We've been going for another 58 minutes.

MR. MICELI: Would -- how are you doing? Would you like to take a break?

MR. McCULLY: If you're at a stopping point.

MR. MICELI: I'm at a natural stopping point. I don't -- I think I'd be at a better one to do it later -- I don't think I would be.

THE VIDEOGRAPHER: We are going off the

expectation from FDA. I don't know -- I don't presume it was the case before systemically.

Q. Okay.

A. I know today it's true. Yeah.

Q. Today you --

A. Today in 2018.

Q. You would expect that if clinical trial information was being provided to FDA, you would include all the data sets to go with it?

A. Yes.

Q. But you don't know -- you can't tell me, as a matter of fact, that for TAX316, that the data sets were provided to FDA?

A. No, I cannot say that, especially because I was not the trial statistician. I was not involved in that submission. I only contributed to that labeling discussion.

Q. Okay. Do you know Linda Gustavson?

A. Linda?

Q. Does that name ring a bell?

A. I'm not sure.

Q. Okay. Concerning the statistical analysis plans -- now, are you familiar with what a statistical analysis plan is?

A. Yes.

Q. Okay. And that's the plan that is set up before a clinical trial is done that describes how the data will ultimately be analyzed, correct?

A. Yes.

Q. Okay. Where are statistical data plans kept? What system are they kept on?

A. In DOMASYS.

MR. McCULLY: Object to form.

Q. Okay. On DOMASYS?

A. Yeah.

Q. Okay. Okay. All righty. Let's continue on this e-mail at the top of Page 3. We had gotten through this -- through the sentence that ends that Emanuel -- mentioned by Emanuel below, and the proposed wording is also fine with me.

Then your next statement is: Maybe it would, however, be better to only provide information on alopecia as extracted from Tables 7 -- from Table 7 and Table 47 (respective CSRs) -- that's clinical study reports?

A. Yes.

Q. Okay. -- to avoid generation further questions on other information contained in these tables.

That was your comment, correct?

A. Oh, okay. Those that are, you know, are -- have gone through quality controls by other people and have sufficient quality to be analyzed and reported.

Q. Okay. Just so we're -- just so we're clear, the quality control that you're referring to is something that you have no knowledge of yourself, correct? You weren't part of it?

A. I'm not working on the quality control, no.

Q. Right.

A. Yeah.

Q. So you don't know the integrity of the follow-up that was connected with the women in the GEICAM study?

A. I think I know when data have, you know -- available for analysis, that certain processes has been done to clean those data and that, you know, they are sufficient quality so that they can be passed on to biostatistics for analysis. That, I know.

Q. Okay. I think I understand. I think we're talking about two different issues, and I want to try to clear it up with you.

When you receive data, you understand and believe, particularly within the company you work

for, that that information and data has gone through certain quality control measures that speak to its -- or its validity by the time it gets to you such that you can use it in generating reports, like Table 47 and Table 7?

A. It is more than that. I know it has gone through the appropriate quality test by, you know, the people that are responsible for that, and they are ready for analysis.

Q. Okay.

A. I don't believe. I know.

Q. Okay. Who did it for GEICAM?

A. That, I'm -- I was not involved in that study as study statistician, so I cannot say for sure who did it, you know.

Q. Okay. So the answer is you don't know?

A. The answer is that I know that when the data are studied by biostatistics department, they were clean before.

Q. Okay.

A. And they have sufficient cleaning to be analyzed and reported in a clinical study report sent to an authority.

Q. What steps were taken to do the quality control on the GEICAM study follow-up?

Statistical analysis plan, and it gives the number, 316, and it says "approved."

Correct?

A. Correct.

Q. Okay. Now let's go to Page 4. Okay? Well, Pages -- Pages 2, 3, and 4 of 47 are the table of contents, correct?

A. 2, 3, 4, 5, yeah.

Q. Okay. Let's look at Page 4.

A. Okay.

Q. Under Section 11.7, the title is "reversibility." Correct?

A. Yes.

Q. Okay. Now, reversibility means what?

MR. McCULLY: Object to form.

A. I think I -- yeah. If you, you know, want me to answer that question, I will have to look at 11.7, you know.

Q. Okay. We're going to go to 11.7.

A. Okay. That's --

Q. In fact, let's go there now. It's on Page 30. Okay. Now, reversibility, 11.7, it says: Reversibility of the following adverse events will be analyzed: And the very first one listed is alopecia, correct?

A. Yes.
Q. Okay. Now, you wouldn't be studying reversibility unless the adverse event was either long-standing, persisting, or permanent, correct?
MR. McCULLY: Object to form.
A. No, I don't think so.
Q. Well, say if you didn't use the word -- they didn't -- they used the word "reversibility." They didn't use "not persistent." Correct?
MR. McCULLY: Object to form.
A. I think the statistical analysis plan was written in 2002. We talk about a table generated eight years after, after multiple regulatory discussion.
Q. That's fine. I'm not -- I'm not worried about multiple regulatory discussions or 2002.
A. So --
Q. This is Sanofi's statistical analysis plan.
A. Yeah.
Q. And in 2002, before the last patient was even enrolled in the -- in the study and the first patient was out of the study, they had planned to study the reversibility of alopecia. That's what this document says, right?
A. Yeah.

EXHIBIT L

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

****

IN RE: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY — MDL No. 2740
LITIGATION — Section: "N"(5)
Judge Engelhardt
This Document Relates to: — Mag. Judge North
All Cases

****

CONTINUED VIDEOTAPED DEPOSITION OF
PIERRE MANCINI

Friday, October 12th, 2018
8:30 a.m.

Held At:
DLA Piper UK LLP
160 Aldersgate Street
London, England

REPORTED BY:
Maureen O'Connor Pollard, RMR, CLR, CSR

BY MR. MICELI:
Q. It's on Page 17 --
A. Yeah.
Q. -- of 181 --
A. So --
Q. -- "Safety Population."
A. So again, that document says that safety means a variable that indicate safety population, okay, and the document you show me have "Safety" and a "Y" below it. So whether this represents the full safety population of the study, you know, I cannot say that, you know. I mean --
Q. Certainly. I'm not representing to you that it is the --
A. So --
Q. -- full population of the -- safety population of the study.
A. No.
Q. But let me show you what was Exhibit 25 to your deposition originally, and this is the Table 7 from the final clinical study report that we went over extensively. And at the top center of the page there's a date, 9 September, 2010.

Do you see that?

MR. DEPAZ: Object to the form.

A. I see the document.

BY MR. MICELI:

Q. Okay. And that's Sanofi's final clinical study report that has a date of September of -- it says 9 September, 2010, correct?

MR. DEPAZ: Object to the form.

A. That, I don't know.

BY MR. MICELI:

Q. Well, it's what's on the page.

A. Okay. The date there says 9 September, 2010.

Q. Sure.

And before you analyze data for a clinical study report that's going to be submitted to regulatory authorities, you have to have a data lock date, correct?

A. Yes.

Q. Okay. And the data lock date means that you lock down the data fields in your dataset for that clinical study, correct?

A. We locked -- the database is locked, yes.

EXHIBIT M

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	MDL NO. 2740
	SECTION: "H"
	JUDGE MILAZZO
THIS DOCUMENT RELATES TO: ALL CASES	MAG. JUDGE NORTH

* *

The videotaped CMO 36 trial preservation deposition of DAVID B. MADIGAN, PH.D., VOLUME I, taken in connection with the captioned cause, pursuant to the following stipulations before RITA A. DEROUEN, Certified Court Reporter, Registered Professional Reporter, on November 14, 2022, beginning at 9:57 a.m.

A. I did not.

Q. Okay. All right. When you look at the HER2 status of people who were positive, is there anything about the randomization of those two -- of the HER2 status that would demonstrate objectively that people were sicker in one group or the other?

MR. STRONGMAN:

Objection; form.

A. As I understand it -- I'm not an expert in this. As I understand it, having positive HER2 status is not a good thing. So the two groups are approximately balanced, slightly more in the FAC group than the TAC group, but very closely -- you know, closely balanced.

BY MR. MICELI:

Q. Okay. I'm going to ask this question a little bit differently. Did you look at the randomization as to hypertension, anxiety, and obesity?

A. No.

Q. Okay. Now, once you have a locked clinical trial dataset that is properly randomized and the data is locked, is it ever appropriate to go behind that locked clinical trial data to

answer questions?

MR. MERRELL:

Objection; form.

A. Sorry, behind the lock?

BY MR. MICELI:

Q. Well, what do you rely upon when you're analyzing a locked clinical trial dataset?

A. You're relying on the locked data, right. There's a process that led to -- you know, that involved checking, rechecking every last item of data in the clinical study at a moment in time when the sponsor, the study sponsor, said I'm done, this is it, this is the locked record of this study.

It's hugely important in terms of the regulation of drugs because those locked data lead to regulatory decisions and drug approvals or failure to approve. But they're hugely important in -- it is the central data source for decisions that the regulator makes that then affects people's lives.

So, you know, you cannot have, two years later or two days later or 20 years later, something -- you know, something coming back and saying, never mind, you know, that wasn't actually

A. Broadly speaking, yeah, very similar studies.

Q. Did they -- was the follow-up done exactly the same in both?

A. I'm reluctant to say absolutely yes because there might be tiny differences, I don't know. But generally speaking, these two studies are very, very similar.

Q. Okay. Do the findings of your metaanalysis support a conclusion that a statistical -- strike that.

Do the findings of your metaanalysis support your conclusion of a statistical association and inference of causation between tax -- between docetaxel and permanent chemotherapy-induced alopecia?

MR. STRONGMAN:

Objection; form.

A. Yes.

BY MR. MICELI:

Q. Do you understand the question?

A. Sorry, I said yes.

Q. I'm sorry, you said yes. Okay, thanks.

I want to show you -- if we could go to Exhibit 6 of your -- of this deposition, the

columns as you used for docetaxel? Can you -- let me restate that.

In conducting your FAERS analysis, did you use the exact same search criteria or analytic criteria to conduct the search for each of these chemotherapy drugs?

A. Yeah, I would refer to it as the end point. So I used the exact same -- actually, the same computer program, the exact same code, run the exact same analysis for each of these drugs in turn.

Q. Okay. Did the findings of your FAERS analysis support your conclusion of the statistical association and inference of causation between docetaxel and permanent chemotherapy-induced alopecia?

MR. STRONGMAN:

Objection; form.

A. Yes, it's important.

BY MR. MICELI:

Q. Why is that?

A. So it's good practice in these -- in these -- when addressing these kind of questions to look at different strands of evidence. They vary in terms of their force, their scientific

force. But it's good practice to look at different strands of evidence. This is one of them.

Q. Okay. In your experience in conducting FAERS analyses, have you ever done this for pharmaceutical companies?

A. Yes.

Q. Okay. Do pharmaceutical companies and the FDA use these types of analyses to look for safety signals?

MR. MERRELL:

Objection to form.

A. Yes.

BY MR. MICELI:

Q. And do they use these types of safety signals to look for increased risk -- supporting evidence of increased risk of side effects?

MR. MERRELL:

Object to the form.

A. Sorry, I missed the clause there.

BY MR. MICELI:

Q. Do drug companies and the FDA use the FAERS analysis to look for both safety signals and increased risks of causality or supporting evidence of increased risk of causality related to

A. I do.

Q. And did the methodology that you employed, is it at all similar to what Dr. Hangai did in completing this clinical overview?

MR. STRONGMAN:

Objection; form.

A. Yeah, at a sufficiently high level, it's similar. She looked at different strands of evidence.

BY MR. MICELI:

Q. Okay. And concerning the clinical trials -- strike that.

I'm going to talk -- you can put that aside for a moment, Dr. Madigan.

The -- did your review of Sanofi's pharmacovigilance database and the information contained in it inform your opinion on -- pardon me, I want to make sure I mention this correctly. I don't want to operate off of memory.

Do your findings and review of the pharmacovigilance database and your analysis of it support your conclusion of a statistical association and inference of causation between docetaxel and PCIA?

MR. STRONGMAN:

Objection; form.

A. Yes.

BY MR. MICELI:

Q. Now let's talk about the fourth and final strand of evidence that you mentioned earlier today, and that is the observational studies. Can you tell us first -- we talked earlier today about what an observational study is.

Can you tell us how you went about selecting observational studies to review for your analysis.

A. So I conducted a search, I did this in September 2019, of electronic databases of the scientific literature, so PubMed, Embase, and SCOPUS. And I searched -- I searched those databases for relevant studies so I can -- the search terms are in my report.

And then I reviewed the hits, you know, what came back from that search, and I identified four -- four observational studies that were -- were germane.

Q. For the benefit of the juries that may watch this video, the jury that may watch this video, can you tell us what your search terms were and how you went about conducting that.

EXHIBIT N

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	MDL NO. 2740
	SECTION: "H"
	JUDGE MILAZZO
THIS DOCUMENT RELATES TO: ALL CASES	MAG. JUDGE NORTH

* *

The videotaped CMO 36 trial preservation deposition of DAVID B. MADIGAN, PH.D., VOLUME II, taken in connection with the captioned cause, pursuant to the following stipulations before RITA A. DEROUEN, Certified Court Reporter, Registered Professional Reporter, on November 15, 2022, beginning at 8:38 a.m.

Do you see that?

A. I do.

Q. And then I want you to turn to the page ending in 639.

A. Okay.

Q. Which -- here, I'll put it up on the screen.

A. 39?

Q. It's up on the screen if you want to look at it.

A. I don't have it here. I'll look at the screen. Oh, I do have it, never mind. Okay.

Q. Are you with me?

A. Yep.

Q. And we have a follow-up, right? Follow-up 1, do you see that?

A. I do.

Q. And what's the date of this assessment in the follow-up?

A. March 11, 1998.

Q. Or actually, it's --

A. Oh, sorry, sorry, sorry. November 3, 1998.

Q. November 3, 1998, correct?

And so the follow-up as reflected on this

page is November 3, 1998, correct?

A. That's what it seems, yes.

Q. And when we look back at this, the second chart I showed you, the last follow-up for AE was identified as November 3, 1998, correct?

A. Yes.

Q. And I want you to turn the page to the chart for this follow-up for November 3, 1998, and it lists follow-up for clinical adverse experiences.

Do you see that?

A. I see that.

Q. Okay. And alopecia is here.

What box is checked?

A. So "status of adverse event experience: No longer followed due to new chemotherapy regimen startup."

Q. Okay. And so when you look at this page of the report for patient 15002, what you can tell is that as of November 3, 1998, it states that alopecia was no longer followed due to new chemotherapy regimen starting, correct?

A. So it seems.

Q. Right? And that's what Box Number 3 on this form means, correct?

A. Could be.
Q. Okay. And, again, that's consistent with the second chart that we looked at, correct?
A. What's consistent? What do you mean?
Q. Well, the date, the last follow-up for adverse event, the date in the chart that we looked at --
A. Okay.
Q. -- the second chart, matches what we're seeing in the report, fair enough?
A. Okay.
Q. And then if you look forward a few pages, there's a page that ends in 49.
A. Yep.
Q. And it indicates that this patient actually started taking taxol, correct?
A. Maybe, yeah.
Q. And so what we know when you looked under the data and you looked at the case report form is that patient 15002 started on Taxotere and ultimately started taking taxol, correct?
A. Maybe.
Q. At least based on the exhibit in front of you, that's what it indicates, correct?
A. Could be. I don't know these types of

forms, but could be.

Q. And, obviously, the start date of taxol is after the start date for Taxotere, correct?

A. So it seems.

Q. And then if you look forward to what ends in page -- strike that.

If you move forward to the page ending in 54, let me know when you're there.

A. I'm there.

Q. And this indicates a physical examination and patient status as of what date?

A. 25th of July -- excuse me -- 2001.

Q. And you would certainly agree this is well after this patient started taking taxol, correct, based on the exhibit in front of you?

A. So it seems.

Q. And this is after patient 15002 was no longer followed for alopecia because that patient started another chemotherapy, correct?

MR. MICELI:

Object to the form.

A. I don't know -- I cannot know that. I saw a form that you put in front of me that had that box checked. That's all I know.

BY MR. STRONGMAN:

junk out. I want to try to use one with you as well. Have you heard the quote "Lies, damned lies, and statistics"?

A. Yes.

Q. I think it was coined by Mark Twain, wasn't it?

A. I believe so.

Q. Did statistics tell a true story about this Crown study regarding the percentage of people when you look at a non-statistically significant group and compare -- of 12 people and compare it to a group of 265 people, do you expect it to show the truth about a drug?

MR. STRONGMAN:

Objection; form.

A. So technically what I expect is that it has very little statistical power. So a study -- I haven't done the calculation, but, you know, based on my experience, a study of this type probably -- it has very little statistical power, is unlikely to find an effect, if one is there.

BY MR. MICELI:

Q. Okay. I'm jumping around a little bit, and I apologize, Dr. Madigan. But when -- when Mr. Strongman was questioning you and showing you

the documents about a patient in the TAX 316 study that has been switched from Taxotere, or docetaxel, to paclitaxel, and I believe -- I think we've already gone through it. It's back to Exhibit 21 that he showed you --

A. Correct.

Q. -- where a patient was switched from Taxotere, docetaxel, to paclitaxel and questioned you that -- concerning whether or not that patient should have been included in the number 29 demonstrated on Table 7 of the clinical study report.

Do you recall those questions?

A. I recall those questions in general, yes.

Q. And is today the first time you've ever been questioned about that?

A. Not about this general issue. I'm not sure if I ever saw this document before, Exhibit 21. But the general issue I've certainly been questioned about before.

Q. Have you -- when have you been questioned about that?

A. Oh, I don't know exactly, but in prior depositions.

Q. Okay. And based upon those prior -- that

prior series of questioning on that topic, did you go back and try to figure out how many patients in the TAC arm and how many patients in the FAC arm were switched from docetaxel to another chemotherapy drug?

A. Yes.

Q. And what did -- what was that called in your analysis when they were switched to a second chemotherapy regimen?

MR. STRONGMAN:

Object to the form.

A. I called it chemo 2.

BY MR. MICELI:

Q. Okay. And how many people received chemo 2 in the TAC arm?

A. That I don't have at my fingertips. I could find -- I could recover that, do the analysis again.

Q. Let me ask you this: How many people in the 29 received chemo 2?

A. Of the 29, nine of those patients were -- had chemo 2, what we're calling chemo 2.

Q. And how many patients in the 16 on the FAC arm received chemo 2?

A. Also nine.

Q. So if we take those nine people out, you end up with 20 and 7, is that respectively -- for TAC and FAC?

A. Yes.

Q. Okay. And have you assessed whether such a finding, 20 versus 7, is statistically significant?

A. Yes.

MR. STRONGMAN:

Objection; form and undisclosed opinion.

THE COURT REPORTER:

I'm sorry, objection; form, what?

MR. STRONGMAN:

Undisclosed opinion.

Go ahead.

A. So yes. So I've done that analysis where you just remove the patients who had second -- had chemo 2, and, indeed, then the difference between TAC and FAC is statistically significant.

BY MR. MICELI:

Q. In TAX 316 alone?

A. In TAX 316 alone.

Q. Okay. Just out of curiosity, because you were questioned about whether or not you published

EXHIBIT O

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

****

IN RE: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY LITIGATION

Docket No. 16-MD-2740
Section H
New Orleans, LA
Tuesday, November 16, 2021

Relates to: Elizabeth Kahn
16-CV-17039

****

TRANSCRIPT OF TRIAL PROCEEDINGS
HEARD BEFORE THE HONORABLE JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE
DAY 6, MORNING SESSION

APPEARANCES:

FOR THE PLAINTIFF:

BACHUS & SCHANKER, LLC
BY: DARIN L. SCHANKER, ESQ.
J. KYLE BACHUS, ESQ.
101 W. Colfax Ave., Suite 650
Denver, CO 80202

GIBBS LAW GROUP, LLP
BY: KAREN B. MENZIES, ESQ.
ANDRE MURA, ESQ.
6701 Center Drive West, 14th Floor
Los Angeles, CA 90045

DAVID F. MICELI, LLC
BY: DAVID F. MICELI, ESQ.
P.O. Box 2519
Carrollton, GA 30112-0046

PENDLEY BAUDIN & COFFIN
BY: CHRISTOPHER L. COFFIN, ESQ.
JESSICA A. PEREZ, ESQ.
2505 Energy Centre
1100 Poydras St.
New Orleans, LA 70163

A. I do.
Q. Okay. And so if you count up all of the numbers under the TAC arm there, and it goes to the next page and then we have the FAC arm. If you count them up you're going to get the 29 and 16 that you've talked about; fair enough?
A. Okay.
Q. And you know, Doctor, when it comes to defining ongoing alopecia in this study, if somebody, like, had alopecia the last time they were seen but then passed away, it could be considered ongoing in this study, correct?
A. Yeah. It's through the end of follow-up for, you know, however that ends.
Q. And somebody could be given additional chemotherapy medication, like Taxol for example if they had an allergic reaction to Taxotere, but they could still be considered as ongoing for adverse events in this study, correct?
A. So they -- you know, somebody could have another round of chemotherapy because of a relapse, so they, you know, they -- yeah, and say their alopecia continued after that, they could be considered as ongoing. But to that specific point, that's actually something I looked at. There are 9 patients -- amongst the 29 and the 16, 9 of these people had what's called "Chemo 2," and 9 of these people had Chemo 2. So it's 9 people -- 9 out of the 29 and 9 out of the 26. So, you know, if -- if you were to not include those people, if -- so I am not arguing for this -- but if you were

to do that, you would then instead of having 29 and 16, you would have 20 and 9, which is, as it happens, is actually statistically significant in and of itself.

Q. Fair enough. And, Doctor, my question was just that you could have somebody get additional chemotherapy that wasn't Taxotere and they could still be counted as ongoing in the chart?

A. Right. And my answer was to say I'm aware of that and I did an analysis --

Q. Very good.

A. -- to address that question.

Q. And you could also have patients that are "lost to follow-up." What's "lost to follow-up" mean?

A. That you're lost to follow-up. You know, it happens. I don't know if it happened in this study, but people moved city and can't be found, stuff like that.

Q. And you can have patients that are lost to follow-up that are also counted as having ongoing adverse events in the study, correct?

A. You could. I mean, the follow-up varied. For, you know, many of the patients it was eight, nine, ten years and for other patients it was, you know, less than that.

Q. And you could also have a situation where a patient, say, had an allergic reaction, started a new chemotherapy, and so the study didn't follow an adverse event after that point but did follow the patient to see if they survived. That could happen, correct?